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TRANSFUSION REACTIONS CAUSED BY ACQUIRED INTRAGROUP INCOMPATIBILITIES

CAPTAIN GUY DARRELL AYER JR. AND CAPTAIN WALTER FRED KAMMER
MEDICAL CORPS, ARMY OF THE UNITED STATES

Routine grouping and cross matching of blood of donors and of recipients [1] enable the laboratory to supply compatible blood for most transfusions. However, blood that is satisfactory by the usual technic may produce serious, even fatal, hemolytic reactions in patients receiving repeated transfusions.[2] It has been shown that such intragroup incompatibilities are produced by immune isoagglutinins that develop in the recipient. The agglutinogen present in the blood of the donors is usually the Rh factor, although other factors occasionally may be responsible. Irrespective of the factor involved, the intragroup transfusion reactions in male patients are similar in that they occur after repeated transfusions.

Repeated transfusions are frequently indicated in the treatment of certain types of patients who are transferred finally to Army general hospitals. Therefore, it seems likely that it will be in such institutions that the problem of acquired intragroup incompatibilities will be met most often. From Nov. 8, 1941 to Aug. 31, 1942 there were 2 severe and 25 mild reactions to transfusion at the O'Reilly General Hospital. During this period, 231 transfusions were given to a total of 46 patients. Fourteen of these patients received from 5 to 28 transfusions for a total of 177. Seven of the 14 had no reaction. The other 7 suffered 26 of the 27 reactions. There were 16 pyrogenic reactions (3 major and 13 minor), 7 allergic reactions manifested by mild urticaria, 2 reactions consisting of transient precordial pain and 2 hemolytic reactions. The 2 hemolytic reactions occurred in the same patient after his twenty-seventh and twenty-eighth transfusions and were the result of acquired intragroup incompatibility, in which the agglutinogen was the Rh factor. After the experience with this case, the inadequacy of routine cross matching for demonstrating acquired isoagglutinins was recognized. Thereafter, when prospective recipients were known to have received more than 5 transfusions the centrifuge technic for cross matching was adopted as a routine procedure. Despite this precaution, a second patient suffered a severe reaction from blood that was compatible according to these additional laboratory procedures. The study of these 2 cases serves to illustrate the ways of preventing reactions due to acquired intragroup incompatibility, a transfusion hazard that has been investigated and overcome largely within the past two years.

HISTORICAL ASPECTS

In 1940 Landsteiner and Wiener [3] reported an agglutinable factor in human blood detectable by immune serums for Macacus rhesus blood. Blood agglutinated by this immune serum is designated as being Rh positive blood; that not agglutinated by it is designated as being Rh negative. Subsequently, 3 cases of hemolytic transfusion reaction were reported in which it was found that the patient's serum contained irregular agglutinins giving reactions unrelated to the four blood groups.[4] These reactions corresponded exactly with the reactions on human bloods of the immune serums for Macacus rhesus blood. Wiener and Peters explained the hemolytic reactions as follows: "Their patients, all being Rh negative and receiving Rh positive blood by repeated transfusions, responded to these injections by producing immune isoantibodies. While at first the foreign Rh positive blood was eliminated from the body without the occurrence of noticeable symptoms, after the isoantibodies were formed subsequent transfusions resulted in hemo-

From the Laboratory and Medical Services, O'Reilly General Hospital, Springfield, Mo.

1. Methods for Laboratory Technicians, War Department, Technical Manual 8-227, Washington, D. C., Government Printing Office, 1941, p. 301.

2. Wiener, A. S.: Hemolytic Transfusion Reactions: I. Diagnosis with Special Reference to the Method of Differential Agglutination, Am. J. Clin. Path. **12**:189 (April) 1942.

3. Landsteiner, K., and Wiener, A. S.: An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood, Proc. Soc. Exper. Biol. & Med. **43**:223 (Jan.) 1940.

4. Wiener, A. S., and Peters, H. R.: Hemolytic Reactions Following Transfusions of Blood of the Homologous Group, with Three Cases in Which the Same Agglutinogen Was Responsible, Ann. Int. Med. **13**:2306 (June) 1940.

lytic reactions of progressively increasing severity, in one case resulting in death."

Recently it has been pointed out that anti-Rh serums are not identical and that blood from a single person may be Rh positive according to one serum and Rh negative when tested with another serum.[5] This introduces one factor which makes it impractical for a laboratory with limited facilities to attempt to prepare a roster of donors with Rh-negative blood for use in cases in which repeated transfusions are indicated for persons with Rh-negative blood. Furthermore, not all acquired intragroup incompatibilities are explained on the basis of the Rh factor. It has been demonstrated that intragroup reactions occur in patients with Rh-positive blood after repeated transfusions.[6] In the blood of such a patient, compatible with that of a donor by ordinary cross matching, an irregular agglutinin is demonstrable in vitro by a centrifuge technic at refrigerator or body temperature. Finally, even these special laboratory methods fail to demonstrate the presence of acquired agglutinins in some cases and the hemolytic transfusion reaction gives the first sign of the existence of the incompatibility.[6]

REPORT OF CASES

CASE 1.—*Anti-Rh agglutinin.*

C. P., a 25 year old white man with five years of service, was admitted to O'Reilly General Hospital May 1, 1942, by transfer from a station hospital which he had entered April 14, 1942, because of a severe sore throat. For this he had received sulfanilamide (1 Gm. four times a day). On April 22 the treatment was discontinued because of gingival bleeding and ulcers of the oral mucous membrane. At this time the red blood cells numbered 2,190,000 per cubic millimeter and the white cells 1,850; the hemoglobin content was 7 Gm. per hundred cubic centimeters. Between April 22 and May 1 he was given 5 blood transfusions of about 300 cc. each, without incident. The past medical history disclosed that the patient had a penile chancre in October 1941. A dark field examination at that time gave positive results, and routine antisyphilitic therapy was started immediately. The last intravenous injection of an arsenical was administered April 30, 1942. At no time was the Kahn or Wassermann reaction positive. He had received a yellow fever inoculation (lot 335) in February 1942.

On physical examination the patient was acutely ill and there was pallor of the skin. The temperature was 101 F., the pulse rate 96 and the respiratory rate 24. There were large necrotic ulcers scattered through the mouth, and abundant pus exuded from the gingival margins. The heart and lungs were within normal limits. The blood pressure was 122 systolic and 80 diastolic. The liver and spleen were not palpable. Numerous petechiae were scattered over the body surface.

Laboratory studies on May 1, 1942 revealed 2,320,000 red blood cells per cubic millimeter and 1,050 white cells and 9.2 Gm. of hemoglobin per hundred cubic centimeters. A differential white cell count showed 82 per cent mature lymphocytes, with no immature forms. The platelet count was 64,000, the coagulation time six minutes and fourteen seconds, the bleeding time thirty-five seconds and the icterus index 6. The Kahn reaction was negative. Roentgenograms of the chest and electrocardiograms gave normal findings. Aspiration biopsy of sternal marrow on June 25, 1942 showed hypoplastic marrow.

TABLE 1.—*Transfusion Record of C. P. (Group O)* *

Date	Donor	Group	Amount, Cc.†	Reaction
5/ 4/42	BW	O	500	None
5/ 6/42	PEN	O	500	None
5/ 8/42	ORA	O	500	None
5/10/42	SRA	O	500	None
5/12/42	RIA	O	500	None
5/14/42	DPB	O	500	None
5/16/42	HJO	O	500	None
5/19/42	LRC	O	500	None
5/21/42	DLD	O	500	None
5/23/42	LHR	O	500	None
5/25/42	JSL	O	500	None
5/28/42	EMC	O	500	None
5/31/42	HWC	O	500	None
6/ 3/42	GMD	O	500	Reported on chart as "slight" reaction following transfusion (nature not stated)
6/ 5/42	LWH	O	500	None
6/ 8/42	WCK	O	500	None
6/10/42	LEA	O	500	None
6/12/42	CJFE	O	500	None
6/14/42	WDK	O	500	None
6/18/42	PH	O	500	None
6/21/42	PJL	O	500	None
6/24/42	FAP	O	500	None
6/27/42	GOT	O	500	None
6/30/42	RWH	O	500	None
7/ 3/42	DJM	O	500	None
7/ 7/42	RIE	O	500	None
7/ 9/42	WNO	O	500	Severe chill 1 hour afterward; temperature 104 F.; patient noticed urine was dark after chill
7/12/42	EAD	O	3 to 5	Following introduction of needle and giving of 5 cc. of blood, patient complained of tenseness in mediastinum, difficulty in breathing and pain in lumbar region; presented clinical picture of mild shock; transfusion immediately stopped, temperature rose to 103 F.

* From April 22, 1942 to May 2, 1942 five transfusions of 300 cc. each were given every other day at a station hospital.
† The indirect citrate method was used for all transfusions.

The therapeutic program consisted initially of repeated blood transfusions and administration of pentnucleotide and of yellow bone marrow. Use of the last two remedies was stopped after seven days, since no beneficial results had been obtained. Transfusions of 500 cc. of blood were given every second or third day for a total of 28. The patient's blood was of group O, and that of all the donors was also of group O (table 1). On June 10, 1942, after 21 transfusions had been given, it was noted that the liver and spleen were palpable, and on June 12 jaundice became manifest. The icterus index gradually increased to 228 on July 19. The hepatitis was treated by daily administration of 1,000 cc. of 15 per cent dextrose solution intravenously, administration of thiamine hydrochloride (5 mg. four times a day) and

5. (*a*) Wiener, A. S.: Hemolytic Transfusion Reactions: III. Prevention, with Special Reference to the Rh and Cross-Match Tests, Am. J. Clin. Path. **12**: 302 (June) 1942. (*b*) Davidsohn, I., and Toharsky, B.: The Rh Blood Factor: An Antigenic Analysis, ibid. **12**:434 (Aug.) 1942.

6. Wiener, A. S.; Silverman, I. J., and Aronson, W.: Hemolytic Transfusion Reactions: II. Prevention, with Special Reference to a New Biological Test, Am. J. Clin. Path. **12**:241 (May) 1942.

a high carbohydrate, high protein, low fat diet. With this program the jaundice, splenomegaly and hepatomegaly gradually subsided. During this period of deep jaundice transfusions (500 cc.) were continued every second or third day, but the red blood count fell progressively. On July 9, 1942, one hour after a transfusion of 500 cc. (donor WNO), the patient had a severe chill, the temperature rose to 104 F. and he noted that his urine, which had previously been clear, became dark brown. On July 13, 1942 another blood transfusion was started. Approximately 5 to 10 cc. of blood had passed into the vein when the patient complained of severe upper mediastinal tension, dyspnea, low lumbar backache and weakness. The patient obviously was in early shock. The transfusion was immediately stopped and the shock treated. No transfusions were given after July 13. Subsequent to the stopping of the transfusions there was gradual improvement in the blood picture. At the time of the patient's discharge, Feb. 17, 1943, the blood counts and differential counts were essentially normal, except for the platelet count, which remained persistently between 50,000 and 60,000. A study of the bone marrow made on Aug. 5, 1942 showed active hemopoiesis.

In review of the history and course of the condition, it was considered that this was a case of aplastic anemia of undetermined cause, sulfanilamide and arsenic being suspected. During the course of this illness catarrhal jaundice developed, which was not thought to be related to transfusions. It is possible, but not likely, that the anemia and the hepatic disease were caused by the same unknown etiologic agent.

After the first reaction (July 9, 1942), the cross match was checked at room temperature and the compatibility of the donor's blood by that method was confirmed. After the second severe reaction it was felt that further studies were indicated. Within an hour after the reaction, 2 drops of the patient's serum and 1 drop of a suspension of the donor's blood cells were placed in small test tubes. One was incubated at 37 C. for thirty minutes and then centrifuged at 500 revolutions per minute for one minute. Another was placed in ice water in the refrigerator for five minutes and then centrifuged in ice water for one minute at 500 revolutions per minute. In both of these tubes the donor's cells were agglutinated, and some agglutination occurred at room temperature after prolonged standing (one hour). Twenty-seven days later samples of blood from the patient and from donor WNO were sent to Dr. I. Davidsohn, of Chicago, who found that the patient's blood was of group O and Rh negative and demonstrated the presence of anti-Rh agglutinin. Donor WNO was found to have blood of group O and Rh positive. Donor EAD was no longer available for study. This is a case of the development of anti-Rh agglutinins in Rh-negative blood. At first there was simply destruction of the transfused blood, as evidenced by the progressive fall in the red blood cell count despite the transfusions. Finally, hemolytic reactions occurred when the patient was given transfusions with Rh-positive blood.

CASE 2.—*Unidentified agglutinin.*

C. J., a 27 year old soldier, was transferred to O'Reilly General Hospital March 28, 1942 from a station hospital which he had entered March 4, 1942 because of persistent bloody diarrhea. About Feb. 18, 1942 he noted the onset of frequent watery stools that were streaked with blood and mucus. The stools, numbering ten to twelve per day, were preceded by severe abdominal cramps. Physical examination and laboratory studies led to a diagnosis of chronic ulcerative colitis.

The therapeutic program consisted primarily of a nutritious diet and supplementary vitamins. Camphorated tincture of opium contributed little toward controlling the diarrhea. A course of sulfaguanidine caused no improvement. On May 17, 1942, the total serum protein was 6.9 per cent, albumin 2.8 per cent and globulin 4.1 per cent. Transfusions of whole blood and of plasma were given to combat mild secondary anemia and the reversed albumin-globulin ratio of the serum. The patient's blood was of group AB, and that of the donors was of groups AB and group O. He suffered occasionally from urticaria following blood transfusions, but no difficulty was experienced in obtaining compatible donors until Aug. 11, 1942. At this time the patient's serum hemolyzed the red cells of two donors with blood of group AB, but the blood of the third donor (SPS) was compatible and the patient had no ill effect from the transfusion other than slight itching of the skin. Between August 11 and September 3, 10 transfusions of plasma were given while the laboratory searched vainly for a donor. Fifteen consecutive donors with blood of group AB were rejected because the patient's serum hemolyzed the donor's red cells (only at incubator temperature). On September 3 a donor (LFF) was found whose blood was compatible on cross matching at room temperature and by the centrifuge technic at refrigerator and incubator temperatures. The transfusion was given over a period of two and one-half hours. Thirty minutes after its completion there was a severe chill, and the temperature rose to 106.4 F. Urine collected two hours after the chill showed no hemoglobin, while blood obtained at the same time gave an icterus index of 5. The cross matchings were repeated, and there was no agglutination or hemolysis at room, refrigerator or incubator temperatures.

On September 7, samples of blood from the donor (LFF) and the patient were sent to Dr. I. Davidsohn, who found them both to be of group AB and Rh positive. The patient's serum did not agglutinate blood of subgroups A, B or A_2B, nor did it agglutinate or hemolyze the offending donor's blood at room temperature, 37 C. or refrigerator temperature. The patient's blood did, however, contain a cold agglutinin acting at temperatures from 2 to 10 C. There is little likelihood that this cold agglutinin caused the reaction, because the donor's blood was collected, transported and administered warm. There remained the remote possibility that the patient had become sensitized to some constituent of the plasma he was given. Consequently, plasma of the same lot was used for cutaneous tests and for agglutination tests (including centrifuge tests). The reactions to all of these tests were negative.

In spite of the failure to demonstrate evidence of hemolysis in specimens of urine and blood collected two hours after the reaction, this is considered to be a case of acquired intragroup incompatibility in which the unidentified agglutinin was not of Rh factor origin. This warm isoagglutinin was demonstrable in vitro after the patient had received 11 transfusions and then only by use of the centrifuge technic. It produced hemolysis of the red cells of 15 consecutive donors with blood of group AB. After three weeks it was no longer demonstrable in vitro, and its presence was demonstrated only presumptively, by the transfusion reaction. This is the type of

case in which a severe reaction may be prevented by employing the biologic test (to be described).

METHODS OF PREVENTION

Wiener [5a] has recently published methods for demonstrating acquired isoagglutinins and has advocated the use of a biologic or clinical test for the recognition of those intragroup incompatibili-

TABLE 2.—*Transfusion Record of C. P. J. (Group AB)*

Date	Donor	Group	Amount, Cc.*	Reaction
4/ 7/42	TBS	AB	500	None
4/11/42	WFS	O	450	None
4/14/42	AJD	O	500	None
4/16/42	OJC	O	350	Mild urticaria
4/19/42	RED	O	500	None
4/22/42	GD	O	500	None
4/27/42	DWMcG	O	300	None
5/10/12	TKE	O	500	None
5/21/42	TDH	AB	500	Severe urticaria
6/ 3/42	FJM	AB	500	Mild urticaria
7/27/42	CFS	AB	500	Severe urticaria
8/11/42	SPS	AB	370	Mild urticaria; temperature 101 F. after transfusion
8/14/42	Plasma	..	500	None
8/15/42	Plasma	..	500	None
8/16/42	Plasma	..	500	None
8/17/42	Plasma	..	500	None
8/18/42	Plasma	..	500	None
8/19/42	Plasma	..	500	None
8/20/42	Plasma	..	500	None
8/21/42	Plasma	..	500	None
8/22/42	Plasma	..	500	None
8/23/42	Plasma	..	500	None
9/ 4/42	LFF	AB	500	Chill; temperature 104.6 F. 30 minutes after transfusion

* The indirect citrate method was used for all transfusions.

ties that cannot be detected in vitro. This laboratory has adopted modifications of these tests and is using the following system for obtaining donors for patients who have had five or more blood transfusions:

Cross Matching:

1. Routine grouping and cross matching at room temperature (read at the end of thirty minutes).

Warm Centrifuge Test:

2. (*a*) Put 1 drop of the patient's serum plus 1 drop of the donor's cell suspension in a small test tube. (*b*) Put 1 drop of the patient's serum plus 1 drop of the patient's cell suspension in a small test tube. (*c*) Incubate *a* and *b* at 37 C. for thirty minutes and then centrifuge for one minute at 500 revolutions per minute in water at about 42 C.

Cold Centrifuge Test:

3. (*a*) Put 1 drop of the patient's serum plus 1 drop of the donor's cell suspension in a small test tube. (*b*) Put 1 drop of the patient's serum plus 1 drop of the patient's cell suspension in a small test tube. (*c*) Place in ice water for five minutes and then centrifuge one minute at 500 revolutions per minute in ice water.

Reading:

4. Take the tubes from the centrifuge and gently agitate. Pour a drop from each tube on a slide and examine microscopically for agglutination.

Interpretation:

5. When no agglutination occurs in any of the tubes, the donor's blood is considered compatible. When agglutination occurs in either or both of the tubes containing the patient's serum and the donor's cells, no agglutination occurring in the control tubes (*2b*, *3b*), the donor is rejected, the procedure having demonstrated the presence of isoagglutinins. When agglutination occurs in both of the tubes at refrigerator temperature (*3a*, *3b*), the reaction is interpreted as due to a cold autoagglutinin, and the donor may be used. However, to prevent a reaction from an irregular isoagglutinin that may be masked by the action of the autoagglutinin, the transfusion officer is advised to employ a modified biologic test. The technic employed is as follows: The patient is given 50 cc. of the donor's blood and is observed for one hour. During this period any urine passed is collected and examined for hemoglobin. If the patient shows no evidence of reaction in an hour and the urine no evidence of hemoglobin, the remainder of the blood is given.

The biologic test finds its greatest usefulness in demonstrating incompatibilities that are not evident in vitro. When a recipient has suffered a hemolytic reaction to a previous transfusion or when the recipient has been found by centrifuge tests to have acquired isoagglutinins for blood of the same group, the biologic test is never omitted even though the blood of the donor used is compatible by routine cross matching and centrifuge tests. Similarly, any severe reaction to a previous transfusion is sufficient indication for its use.

COMMENT

Since the centrifuge and the biologic test have been in use in this general hospital (Sept. 15, 1942 to Jan. 15, 1943), 108 transfusions have been given to 42 patients without serious reaction. There have been 6 allergic and 5 pyrogenic reactions (2 major, 3 minor). Seven patients have received 5 or more transfusions for a total of 63. It has been necessary to reject 18 donors because of positive reactions to centrifuge tests, and 1 patient received a biologic test because of the presence of cold autoagglutinins.

The advantage of this regimen in safeguarding patients receiving repeated transfusions in general hospitals lies in its simplicity and its inclusiveness. Although it does not provide identification of the responsible agglutinogen, the regimen permits the recognition of the presence of acquired incompatibility, whether it be due to the Rh factor or to some other rarer agglutinogen. Finally, it makes possible the selection of a donor whose blood lacks the offending agglutinogen.

THIAMINE METABOLISM

WITH PARTICULAR REFERENCE TO THE ROLE OF THE LIVER AND KIDNEYS

ROBERT H. WILLIAMS, M.D., AND GROSVENOR W. BISSELL, M.D.
WITH THE ASSISTANCE OF JEAN B. PETERS
BOSTON

Banga, Ochoa and Peters [1] have shown that most of the biologic activity of thiamine is exerted only when the latter exists in the form of diphosphothiamine. All of the nucleated cells of the body have been thought to possess the power to convert thiamine to diphosphothiamine,[2] the liver [3] and the kidney [4] possessing this activity more than the other tissues. Furthermore, these organs have a greater capacity for the dephosphorylation of diphosphothiamine.[5]

These observations introduce an important query as to whether with severe disease of the liver or kidneys there is a disturbance in thiamine metabolism. Certain studies that have been made suggest that such may be the case. For example, Borson [6] found that 3 patients with hepatic cirrhosis, excreted a distinctly larger percentage of a standard test dose of thiamine than did his normal subjects. He suggested that the damage of the liver might cause a decrease in the phosphorylation of thiamine and lead to a decrease in the storage and utilization of this vitamin. A somewhat similar phenomenon was observed by Williams, Egana, Robinson, Asper and Dutoit [7] in thyrotoxic patients. They found that some of these patients excreted normal amounts of thiamine in the urine even when the diphosphothiamine content of the blood was subnormal. The frequent existence of impaired hepatic function in thyrotoxicosis and the resulting decrease in the phosphorylation capacity of the liver were suggested as one explanation for the inefficient thiamine economy.

Thiamine deficiency is often present in patients with hepatic cirrhosis. A history of a low thiamine intake is usually obtained, but this may not be the only factor involved in the reduction of storage of the vitamin. Since thiamine is used in the treatment of hepatic cirrhosis, it is of interest to know more about its utilization in these patients.

Less attention has been paid to the relationship of disease of the kidney to thiamine metabolism. However, it has been observed in patients with renal disease [8] and with congestive heart failure [9] that a subnormal quantity of a test dose of thiamine is excreted.

In an effort to elucidate further the role of the liver and the kidneys in thiamine storage, we have studied certain phases of thiamine metabolism in persons with severe disease of these organs.

PLAN OF STUDY

It was our belief that if the liver and the kidneys play an important role in the phosphorylation of thiamine it might be possible to demonstrate an impairment in this process in persons with severe disease of the liver or kidneys by administering a standard amount of thiamine and determining the blood levels of it frequently. Furthermore, the capacity for dephosphorylation perhaps can be estimated by administering a standard amount of diphosphothiamine and comparing its rate of breakdown with that in health.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

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2. Goodhart, R. S., and Sinclair, H. M.: Estimation of Cocarboxylase (Vitamin B_1 Diphosphate Ester) in Blood, Biochem. J. **33**:1099, 1939.

3. Ochoa, S.: Enzymic Synthesis of Cocarboxylase in Animal Tissues, Biochem. J. **33**:1262, 1939.

4. Westenbrink, H. G. K., and Goudsmit, J.: Investigations on the Aneurin and Cocarboxylase Content of Animal Tissues, Estimated by the Thiochrome Method, Enzymologia **5**:307, 1938.

5. Ochoa, S., in Evans, E. A., Jr.: The Biological Action of the Vitamins: A Symposium, Chicago, University of Chicago Press, 1942, pp. 17-42.

6. Borson, H. J.: Clinical Application of the Thiochrome Reaction in the Study of Thiamin (Vitamin B_1) Deficiency, Ann. Int. Med. **14**:1, 1940.

7. Williams, R. H.; Egana, E.; Robinson, P.; Asper, S. P., and Dutoit, C.: Alterations in Biologic Oxidation in Thyrotoxicosis: I. Thiamine Metabolism, Arch. Int. Med. **72**:353 (Sept.) 1943.

8. Najjar, V. A., and Holt, L. E., Jr.: Studies in Thiamin Excretion, Bull. Johns Hopkins Hosp. **67**: 107, 1940.

9. Robinson, W. D.; Melnick, D., and Field, H., Jr.: Urinary Excretion of Thiamin in Clinical Cases and Value of Such Analyses in Diagnosis of Thiamin Deficiency, J. Clin. Investigation **19**:399, 1940.

All of the subjects with severe disease of the liver had Laennec's cirrhosis. They had had pronounced ascites, but at the time the test was performed little or no fluid was present. No patient was jaundiced at the time of the test. No more than a slight anemia was present in any subject, and there was no leukocytosis. Although several of these patients were probably deficient in thiamine at the time they were admitted to the hospital, each patient was given 10 mg. or more of thiamine hydrochloride per day for at least one week. In an effort to avoid having these patients supersaturated with thiamine at the time of the test, the supplementary thiamine was not given for at least three days preceding the test. Evidence of pronounced impairment of hepatic function was secured by means of the hippuric acid test and the bromsulphalein test. All patients had been hospitalized for several weeks preceding the test, and on the day of the latter they were kept in bed in a fasting and resting state.

All of the subjects with severe disease of the kidneys had well defined chronic nephritis with pronounced uremia. None of these patients had more than a mild degree of congestive heart failure. The same precautions for avoiding thiamine deficiency were taken as in the group with cirrhosis. There was little deviation of the blood from normal, except for moderate anemia in 1 patient.

The normal subjects were college students. On the day of the test the student came to the hospital without breakfast and with as little exertion as possible. He then lay down for thirty minutes before the test was begun and remained in a basal condition until the test was completed.

After a fasting specimen of blood was taken, 15 mg. of thiamine hydrochloride was injected intravenously during a period of exactly two minutes.[10] Immediately after the injection a sample of blood was taken from the opposite arm. Samples, about 15 cc. each, were taken subsequently at six minutes, fifteen minutes and one hour. Twice this amount was obtained as the fasting specimen in order that a thiamine recovery experiment could be performed. Potassium oxalate was used as an anticoagulant, the final dilution being 0.2 per cent. Immediately after collection each sample of blood was placed in a pan of ice and kept there until the analysis for the thiamine and diphosphothiamine was begun, about fifteen to thirty minutes later.

The experiment was repeated with other groups of normal, cirrhotic and nephritic persons, 15 mg. of cocarboxylase [11] (diphosphothiamine) being used instead of thiamine. In this experiment the blood cells and the plasma were analyzed individually for the content of thiamine and diphosphothiamine.

The normal subjects were studied also for changes in the thiamine and diphosphothiamine levels of the blood after the administration by mouth of 15 mg. of thiamine in about 3 ounces (90 cc.) of water.

Immediately on the completion of each test the subject was requested to empty his bladder. The urine was preserved with glacial acetic acid and analyzed for thiamine.

Methods of Thiamine and Diphosphothiamine Analysis.—The method employed for the estimation of thiamine in the urine was described by Egana and Meiklejohn.[12] This method is a modification of the ones used by Jansen,[13] by Hennessey and Cerecedo [14] and by Harris and Wang.[15] It depends on the oxidative conversion of thiamine to thiochrome in the presence of alkaline ferricyanide, giving a bluish fluorescence under ultraviolet radiation, which can be quantitated by a comparison with a set of standards. This method has proved to be relatively accurate for the estimation of thiamine in the urine. The total twenty-four hour excretion of normal persons has been found to range from 35 to 250 micrograms.

In the estimation of the thiamine and the diphosphothiamine content of blood we have used the methods of Egana and Robinson.[16] The technic is similar to that for the determination of thiamine used on urine. The content of diphosphothiamine in the blood is similar to that in the urine. It is estimated on the same specimen of blood as is used for the determination of thiamine. This is possible because diphosphothiamine is converted into diphosphothiochrome in the presence of alkaline ferricyanide and the diphosphothiochrome can be separated from thiochrome, owing to the insolubility of the former in isobutyl alcohol. The standards for diphosphothiochrome are prepared by running known amounts of diphosphothiamine through the same procedure as the unknown. The amount of blue fluorescence is compared with standards, as in the case of thiochrome, and thereby the amount of diphosphothiamine determined.

Great care must be taken to avoid any hemolysis, since it has been our experience as well as that of others [17] that this leads to large errors in the estimations of thiamine and diphosphothiamine.

The thiochrome method is not as accurate when applied to blood as when applied to urine. In the former there are more interfering substances and the percentage of recovery of added thiamine is more variable. Similar difficulties are encountered with the determination of diphosphothiamine. However, these methods may be used for the estimation of pronounced relative changes such as we are presenting in this study.

RESULTS

(*a*) *Results of Administration of Thiamine.*—After the administration of 15 mg. of thiamine hydrochloride by mouth to the normal subjects a rapid absorption of this substance was evidenced by a distinct rise in the thiamine level

10. Originally the test dose was 5 mg., but it was increased to 15 mg. because the former amount did not cause as much change in the thiamine level of the blood as we desired. We preferred not to use a larger dose than necessary.

11. The cocarboxylase was supplied by Merck & Co., Inc.

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of the blood six minutes later (chart 1). The diphosphothiamine rose concomitantly and continued to increase for fifteen to thirty minutes; at the end of one hour it was still above normal.

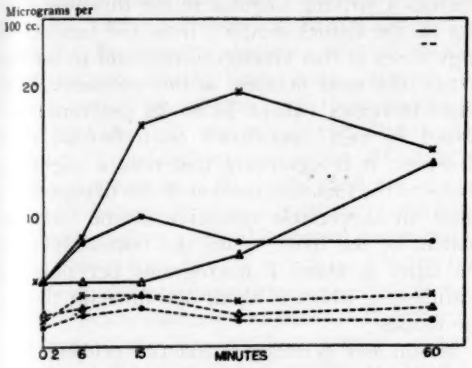

Chart 1.—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of whole blood of 3 normal subjects following the oral ingestion of 15 mg. of thiamine hydrochloride.

The elevation of the thiamine level was of less degree than that of the diphosphothiamine, and it tended to return to normal more quickly. The amount of thiamine excreted in the urine was 0.6 per cent (range 0.3 to 0.8 per cent) of the injected dose.

When thiamine was administered intravenously to normal subjects the changes in the blood

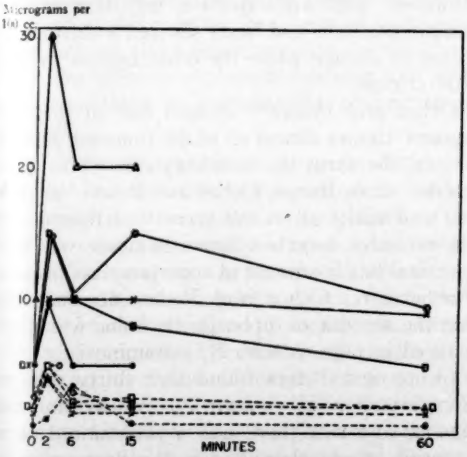

Chart 2.—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) levels of the blood following the intravenous injection of 15 mg. of thiamine hydrochloride into 5 normal subjects. Each injection was given during a period of two minutes.

took place much more quickly (chart 2) than when it was given by mouth.[18] The thiamine level of the blood reached a peak immediately on completion of the injection, but within six minutes it was normal. The rapid rate of phosphorylation was demonstrated by the large amount of diphosphothiamine found in the two minute sample. Thereafter the level declined, although in 2 instances it was still elevated at the end of an hour.

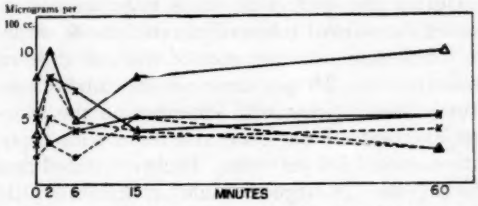

Chart 3.—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) of the blood of 3 patients with hepatic cirrhosis given intravenously 15 mg. of thiamine hydrochloride.

In the patients with cirrhosis (chart 3) there was distinctly less rise in the diphosphothiamine content of the blood than occurred in the normal group (chart 2). This fact plus the slightly greater rise in the thiamine level of the patients with cirrhosis suggests that phosphorylation had taken place less readily, as discussed later.

In patients with nephritis (chart 4) the rise in the thiamine level developed more slowly than in the normal subjects, but the level eventually reached about the same height. This delay may have been due to an increase in the circulation

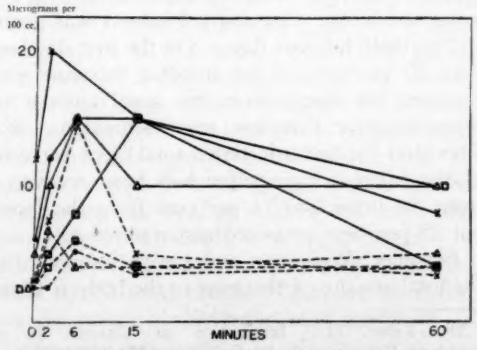

Chart 4.—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) of the blood of 4 patients with chronic nephritis given 15 mg. of thiamine hydrochloride intravenously.

time. The amount of diphosphothiamine formed is essentially the same as in the normal group.

Although in the three groups of subjects a striking increase in the diphosphothiamine content of the blood occurred after the injection of

18. The great variability in the responses of the normal subjects, as well as in those of the abnormal ones, is shown by the curves in the figures. Therefore, in our interpretations we have considered the trends rather than the specific curves.

thiamine, this rise was not of sufficient magnitude to account for more than 5 per cent of the amount injected. This leads to the questions as to (1) whether most of the thiamine was excreted in the urine, (2) whether it was stored in the tissues or (3) whether it was broken down to substances which do not give the thiochrome reaction.

During the hour that these tests were conducted the normal subjects excreted in the urine, on the average, 0.6 per cent of the oral dose of thiamine and 2.8 per cent of the intravenous dose. The patients with cirrhosis on the average excreted 4.7 per cent, and those with nephritis excreted 1.4 per cent. Tauber [19] stated that the ingestion of large amounts of vitamin B_1 did not result in excretion of cocarboxylase in the urine, as we have also noted. Therefore, the amount of thiamine excreted in the urine would not account for much of the administered thiamine. Furthermore, if the pyrimidine accelerator of yeast fermentation [20] were also included, this would not account for much more of the vitamin. As to how much of the thiamine was broken down during the period of observation, the present data are inadequate for a good estimation.

The chief consideration is storage of thiamine —its rate of storage, site and extent. The work of Borsook and associates [21] is of interest in this connection. They injected intramuscularly thiamine containing radioactive sulfur and determined the amount of the latter excreted in the urine and feces. One normal subject was given 16 mg. daily for four days. On the first day less than 20 per cent of the injected thiamine was excreted but many times the usual amount of nonradioactive thiamine was eliminated. Six days after the last injection a total of 61 per cent of the injected radiosulfur had been recovered from the urine and 11 per cent from the feces, but 28 per cent remained unaccounted for.

Ferrebee, Weissman and Owen [22] found that the total amount of thiamine in the body is about 25 mg., the heart containing about 2 to 3 micrograms per gram, the skeletal muscle 0.5 microgram and the liver, kidney and brain about 1 microgram each. These investigators found that whereas a striking increase in the thiamine content of the tissues resulted from the feeding of large doses of this vitamin to rats and to human beings who were deficient in this substance, only slight increases (about 10 to 20 per cent) occurred in men maintained on a normal diet. However, it is significant that only a slight increase in the thiamine content of the tissues could cause an appreciable reduction in the thiamine content of the blood, since the normal level of the latter is about 7 micrograms per hundred centimeters, which is about one fifteenth that of the tissues.

Mason and Williams [23] adduced evidence that an appreciable amount of storage of thiamine may result in man. They fed 2 normal subjects 7.5 mg. of thiamine hydrochloride for thirty-seven days and then placed them for five days on a diet containing 400 micrograms of thiamine and for twenty-two days on a diet which furnished 600 micrograms. Thereafter, the daily twenty-four hour excretion of thiamine was normal, as was the response to a test dose of thiamine.

Leong [24] found that in rats maintained on a normal stock diet the concentrations of thiamine in the various tissues was essentially the same. However, with an excessive ingestion of this vitamin the liver and heart showed a distinct increase in storage while the other organs showed little change.

Ochoa and Peters [25] showed that in rats and pigeons' tissues almost all of the thiamine present was in the form of cocarboxylase. This is of interest, since Banga, Ochoa and Peters [1] showed that essentially all of the activity of thiamine in the oxidative decarboxylation in tissue was proportional to the amount of cocarboxylase present. Furthermore, Ochoa and Peters demonstrated that the amount of diphosphothiamine was much reduced in pigeons with B_1 avitaminosis.

Ochoa and Peters found that thirty minutes after injection of vitamin B_1 into avitaminous pigeons and rats there was a pronounced accumulation of cocarboxylase in the liver, whereas

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little or no increase developed in the skeletal muscle, heart or brain. The level of cocarboxylase in the liver could not be made to rise much above normal. Normal animals given thiamine had only a slight rise in the cocarboxylase of the tissues. Ochoa [3] obtained somewhat similar results for the in vitro synthesis of cocarboxylase from thiamine, using liver, brain, intestine and breast muscle of pigeons. Of these tissues the liver was the only one which exhibited a good capacity to phosphorylate added thiamine to diphosphothiamine. He found that the amount of synthesis soon reached a maximum, which was generally slightly above the normal concentration of cocarboxylase, beyond which no greater concentration of diphosphothiamine resulted, no matter how much thiamine was added. The maximal synthesis in the liver resulted in thirty to sixty minutes, but a short time thereafter the level began to drop. Brain and muscle were found to show less synthesis, but there was no decrease in the amount of cocarboxylase after the maximum was reached. Westenbrink and Goudsmit [4] showed that the kidneys were active in the phosphorylation of thiamine. Goodhart and Sinclair [2] found no evidence of the synthesis of cocarboxylase from thiamine in normal pigeon, ox and human bloods. However, when this vitamin was added to thiamine-deficient pigeon blood, marked synthesis resulted. These investigators also reported that only about 14 per cent of the total thiamine of the blood is in the plasma and essentially all of this is in the free form. On the other hand, almost all of this vitamin in the blood cells is in the form of diphosphothiamine, the white cells containing many times the amount in the red cells.

In summary, the data accumulated thus far suggest that most of the thiamine of the body is phosphorylated before it is stored, the liver and kidneys being particularly active in phosphorylation. The storage can be increased above normal, but there is a limit, which is not much above normal, beyond which no appreciable increase in the stores results. Presumably all tissues share in this accumulation, although not to an equal extent. Immediately after large quantities of thiamine have been injected the liver takes the chief responsibility for the storage and dispensation of this vitamin, permitting its concentration to increase greatly for a temporary period, during which time an establishment of equilibrium is taking place. In this interval some of the diphosphothiamine of the liver is dephosphorylated, the thiamine thereby liberated being carried by the plasma to other tissues, where it is again phosphorylated. It may also be transported in the blood cells, chiefly in the form of diphosphothiamine. An excess of vitamin to that stored in the body is broken down or excreted as thiamine in the urine. As the body stores go below normal, the phosphorylating activity of the kidneys increases and thereby aids in the economy of thiamine by preventing its excretion in the urine.

In attempting to interpret the various changes in the dynamic equilibrium of thiamine on the basis of studies of the blood and urine, certain facts should be emphasized. It has not been established how satisfactory the thiamine level of the blood is as an index of the content of the vitamin in the tissues. The total amount of thiamine in the blood is small, and its concentration in the tissues of the body varies. Furthermore, it is known that when large doses of the vitamin are injected the amount taken out by the tissues varies a great deal.[25]

The fact that in the cirrhotic patients as compared with normal there are less of a rise in the diphosphothiamine, a greater rise in the thiamine and an increased excretion of thiamine in the urine suggests that there is a decrease in the phosphorylation process. If all of the diphosphothiamine of the blood is a result of the phosphorylating activity of the blood cells, it is probable that the liver has an indirect effect on this process (charts 2 and 3). It is possible that the blood cells may receive diphosphothiamine as such from the liver cells, during their passage through the liver. If this hypothesis is correct, in subjects with cirrhosis one would expect a lower level of diphosphothiamine of the blood than one observes in normal subjects, since in the former group there is a decreased blood flow through the liver and a decrease in most of the activities of the liver cells. The in vitro studies of Banga, Ochoa, and Peters [1] with various preparations of brain tissue suggested that cocarboxylase permeates the cell wall not as such but in the form of thiamine, which after entering the cell is phosphorylated. Although it is probable that the phosphorylating action of the kidney is impaired with severe renal disease, there are no definite manifestations of this reflected in the blood.

(*b*) *Results of Administration of Diphosphothiamine.*—After the intravenous administration of 15 mg. of cocarboxylase to normal subjects the plasma level rose rapidly (chart 5) and in 1 subject reached 100 micrograms per hundred centimeters. However, the rapid rate of dephosphorylation is demonstrated by the increase in the thiamine level in the two minute specimen. The thiamine content of the plasma tended to return to normal in six to fifteen minutes, but the diphosphothiamine level remained elevated for more than an hour.

Concomitant with the changes in the plasma, rapid changes occurred in the blood cells (chart 6). A marked increase in the diphosphothiamine was observed in the two minute specimen. There was also a slight increase in the thiamine content

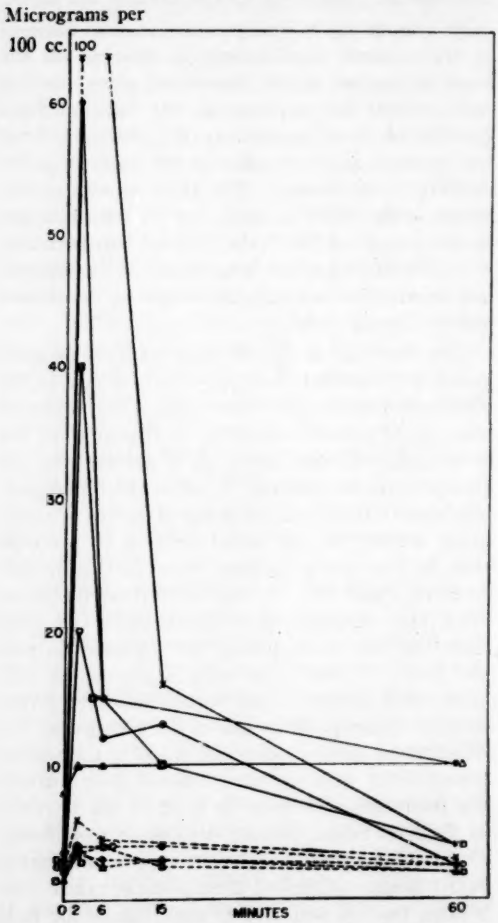


Chart 5.—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of normal blood following the intravenous injection of 15 mg. of cocarboxylase in 4 subjects. The injections were given during a period of two minutes.

of the cells. However, since the increase in the thiamine content of the cells and plasma was relatively small as compared with the increases in the diphosphothiamine content, one is prompted to consider either that diphosphothiamine passes through the cell membrane as such or that it is dephosphorylated and then rephosphorylated at an extremely rapid rate. The latter consideration introduces the query as to how great a part the blood cells alone play in regulating the interconversion of phosphorylated thiamine and free thiamine. Goodhart and Sinclair [2] could not demonstrate in vitro any synthesis of diphosphothiamine from thiamine in normal blood.

Since the liver and kidneys have been demonstrated to be active in dephosphorylating as well as in phosphorylating thiamine, it is important to compare the observations on the normal subjects with those on persons with hepatic cirrhosis and severe nephritis.

In the cirrhotic group (chart 7) there was a distinctly smaller rise in the diphosphothiamine content of the plasma than occurred in the normal group. Furthermore, in the former group the diphosphothiamine had attained normal levels within six minutes, whereas with the latter group it was still elevated at the end of an hour. The diphosphothiamine content of the blood cells also tended to increase somewhat less in the cirrhotic

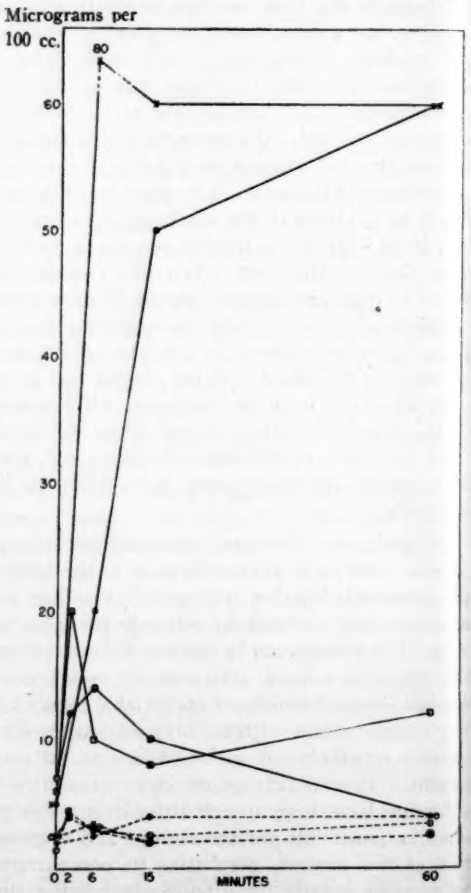


Chart 6.—Same subjects as in chart 5. The curves show the changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the blood cells.

group (chart 8). On the other hand, the plasma thiamine of the cirrhotic group rose more than did that of the normal group. The changes in

the cellular thiamine were similar in the two groups.

The alterations in the thiamine and diphosphothiamine blood levels in the nephritic patients (charts 9 and 10) were somewhat intermediate to those of the normal and the cirrhotic subjects.

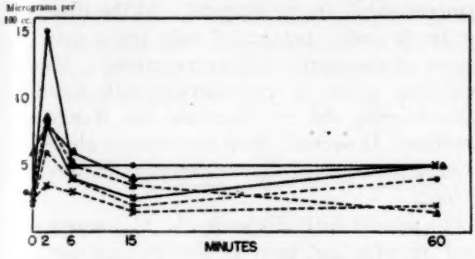


Chart 7.—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the plasma of 3 patients with cirrhosis of the liver given 15 mg. of cocarboxylase intravenously. Compare with chart 5.

During the hour that the test was conducted the amount of thiamine excreted in the urine by the normal subjects was 1.4 per cent of the injected dose of diphosphothiamine; the nephritic group excreted 3.4 per cent. Specimens of urine were obtained from only 1 of the cirrhotic patients. However, he excreted 45 per cent of the injected dose of diphosphothiamine. The urinary thiamine was in the free form and therefore not phosphorylated. In investigating the cause of this striking diuresis of thiamine, it was discovered that one hour before the diphosphothiamine

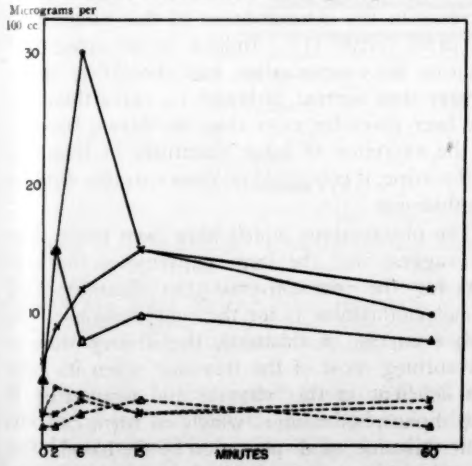


Chart 8.—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the blood cells. Subjects same as in chart 7.

test was made the patient had been given 2 cc. of mercurophylline. Because of this, further observations were made on the effect of mercurophylline on excretion of thiamine.

Effect of Mercurophylline on the Excretion of Thiamine in the Urine.—We first studied the effect of mercurophylline on the excretion of thiamine in the urine of 2 normal subjects. We then studied its effect on 2 patients with slight congestive heart failure and 1 with Laennec's cirrhosis, since these types of patients are the ones which most often are treated with mercurophylline.

The effect of mercurophylline on excretion of thiamine was observed when it was given in conjunction with 15 mg. of thiamine hydrochloride. These two drugs are frequently given together; hence such a study seemed appropriate.

All of the mercurophylline [26] was administered intravenously in 2 cc. amounts two hours before

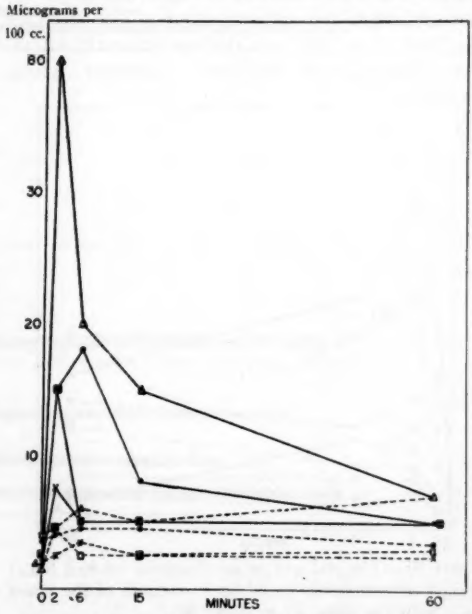


Chart 9.—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the plasma of 4 patients with chronic nephritis given 15 mg. of cocarboxylase intravenously.

thiamine hydrochloride was administered. The latter was injected intravenously in quantities of 15 mg. into all the patients with the exception of patient N. M., who received doses of 1 mg. The urine was collected in glacial acetic acid for twenty-four hours following the injection of thiamine. The same dosage of these drugs was used on the days when they were given singly as when given together.

Normal subject A. M., having fully recovered from pneumonia, was transferred to the metab-

26. The mercurophylline was tested for fluorescence but was found to have none. Therefore, this drug caused no apparent interference with the estimation of thiamine in the urine.

olism ward. Here he was maintained on the regular hospital diet with the addition of 6 tablets of brewers' yeast daily. After one week on such a regimen, estimates were made of the daily excretion of thiamine in the urine. On the fifth day thiamine was given intravenously. In the succeeding twenty-four hours 1.9 mg. of thiamine was excreted (chart 11). On the thirteenth day the subject was given mercurophylline, and during the succeeding twenty-four hours 10 mg. of thiamine was excreted.

Subject S. M., convalescent from an operation for an ingrown toe nail, was transferred to the metabolism ward and was prepared with a dietary regimen, as in the case of A. M. He was given thiamine hydrochloride alone, mercurophylline alone and then the two together. The mercurophylline alone had no definite diuretic effect on the excretion of thiamine. However, when

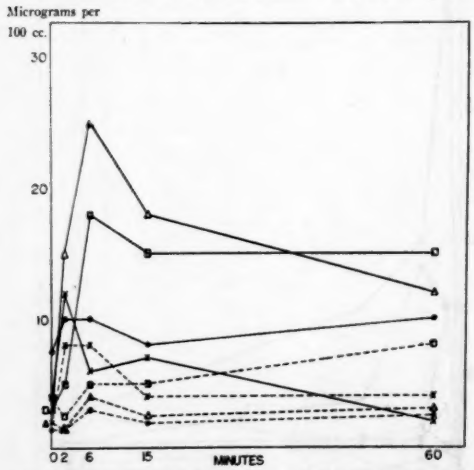


Chart 10.—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the blood cells. Subjects same as in chart 9.

thiamine and mercurophylline were given on the same day there was a distinctly greater excretion of thiamine (1.06 mg.) than when the latter was given alone (0.38 mg.).

Patient W. E., a woman aged 70, had been in the hospital for several weeks with congestive heart failure due to arteriosclerotic heart disease. When we studied her, there was only a slight amount of heart failure. She had received subcutaneously 10 mg. of thiamine hydrochloride for several weeks. The injections were discontinued one week before our studies were begun. A greater diuresis of thiamine resulted when mercurophylline was given on the same day as the thiamine (0.26 mg.) than occurred when the latter was given alone (0.14 mg.). However, when mercurophylline alone was given, the most pronounced diuresis of thiamine resulted (12.6 mg.).

Patient M. U., a woman aged 50, had been in the hospital for several weeks with congestive heart failure because of chronic rheumatic heart disease. Her dietary intake preceding hospitalization was essentially normal, and she was maintained on a "cardiac" diet, without vitamin supplements, while in the hospital. At the time that our studies were conducted only slight manifestations of congestive failure remained. Mercurophylline given in conjunction with thiamine hydrochloride did not increase the diuresis of thiamine. However, when mercupurin alone was given, a pronounced diuresis of thiamine resulted (6.6 mg.).

The patient with cirrhosis (N. M.) was a man aged 35 who had been in the hospital for several weeks. His diet had been supplemented with several vitamins, including thiamine. However, he had received no extra vitamins during the week preceding our studies. When mercurophylline was used alone, there was no definite increase in the amount of thiamine excreted. However, when it was used in conjunction with thiamine, more of this vitamin appeared in the urine (0.28 mg.) than was found after the administration of thiamine alone (0.14 mg.).

Therefore, it is apparent that different subjects excrete variable amounts of thiamine in the urine after the administration of mercurophylline; sometimes this amount is enormous. This increased elimination of thiamine is not due alone to an increase in the volume of urine, since it was found that in several instances there was an increase in the concentration of this vitamin in the urine (chart 11). Indeed, in the urine of 2 subjects the concentration was about fifty times greater than normal, although no extra thiamine had been given for more than ten days. In spite of the excretion of large quantities of thiamine in the urine, it contained no demonstrable diphosphothiamine.

The observations which have been made thus far suggest that the large capacity of the kidney for the interconversion of thiamine and diphosphothiamine is for the conservation of the body's supply of thiamine, the kidney tubules reabsorbing most of the thiamine when its cells are deficient in this vitamin and converting it into diphosphothiamine, which, in turn, can liberate thiamine for dispensation by the blood. On the other hand, when the body is saturated with the vitamin, the kidneys permit its escape in excess quantities. When mercurophylline is administered, the tubular activity of the kidneys can be so disturbed as to permit the elimination of rather large quantities of thiamine in the urine. We found this response to vary a great deal in different subjects.

SUMMARY AND CONCLUSIONS

Thiamine hydrochloride administered to normal subjects by mouth was found to be rapidly absorbed from the gastrointestinal tract and converted into diphosphothiamine within a few minutes.

When 15 mg. of thiamine hydrochloride was given intravenously to normal subjects, an immediate and striking increase in the diphosphothiamine level of the blood was observed. The rapid disappearance of the vitamin from the blood was shown by the fact that the thiamine level of the blood was normal within six minutes and the fact that the total diphosphothiamine of the blood never represented more than about 5 per cent of the injected dose.

In patients with severe hepatic cirrhosis, an impairment in the phosphorylation of the thiamine was demonstrated, but not much disturbance in this mechanism was observed in patients with nephritis.

When 15 mg. of cocarboxylase was administered intravenously to normal subjects, an increase in the diphosphothiamine and the free thiamine of the plasma and the blood cells was observed immediately. The thiamine level rapidly returned to normal, but the diphosphothiamine remained elevated, for more than an hour in some instances. In patients with advanced cirrhosis there was also an immediate increase in the free thiamine level of the blood, but there was much less rise in the diphosphothiamine than occurred in the normal subjects. In patients with severe nephritis, the changes were intermediate between those of the normal and of the cirrhotic groups.

Mercurophylline was found to cause the excretion of a large amount of thiamine. This effect was not due alone to an increased elimination of water, because in some instances the concentration of the thiamine in the urine was many times that found in normal urine.

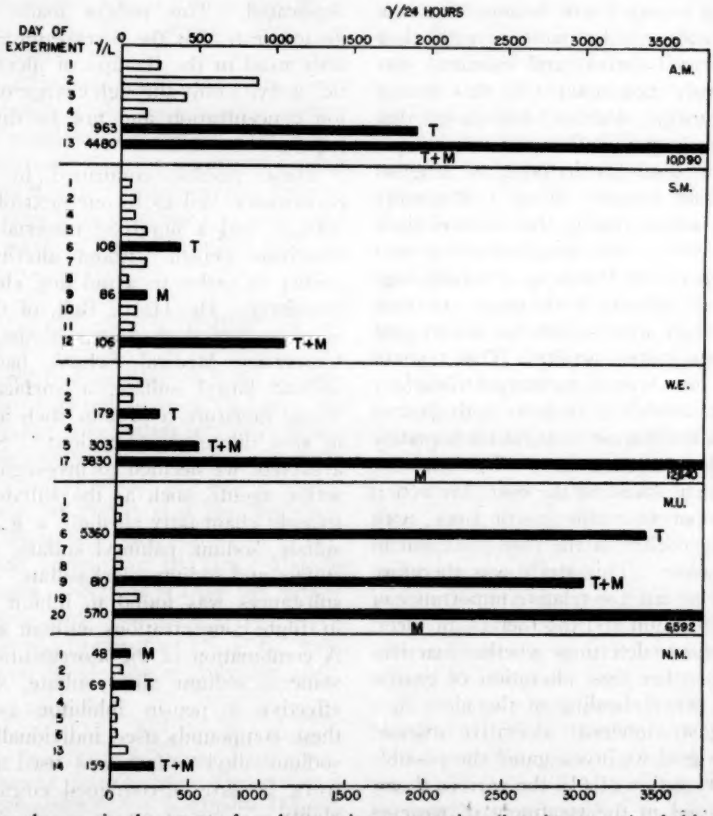


Chart 11.—The changes in the twenty-four hour urinary excretion (in micrograms) of thiamine (T) following the intravenous injection of 2 cc. of mercurophylline (M). When thiamine and mercurophylline were both given, the former was given intravenously two hours after the latter. The amount of thiamine hydrochloride injected was 15 mg. for each patient except N. M., who received only 1 mg. Note that mercurophylline caused a pronounced excretion of thiamine. This increased excretion was not due to just an increased volume of urine. (Values at the left of the solid bars represent micrograms per liter.)

TREATMENT OF GASTRODUODENAL ULCERATIVE DISEASE WITH SODIUM ALKYL SULFATE

A PRELIMINARY REPORT

S. J. FOGELSON, M.D., AND D. E. SHOCH, PH.D.
CHICAGO

Our results from the treatment of gastroduodenal ulcerative disease with sodium alkyl sulfate are being reported now because this new therapy has already enabled patients with ulcer to enter the armed forces, and essential war workers previously incapacitated by this disease to return to industry. Palmer [1] has shown that gastroduodenal ulcerative disease is the major cause of medical disability in both the English and the American forces. Since it is usually present in male adults during the years of their greatest productivity, the impairment of war effort by this prevalent disease is of serious significance. Most patients with ulcer are now being treated by a routine which has for its goal reduction of intragastric acidity. This type of medication has not been completely satisfactory because a large number of patients with gastroduodenal ulcerative disease respond inadequately to this orthodox management. To date the emphasis has been placed on the corrosive action of the acid component of the gastric juice, with almost complete neglect of the role of pepsin in the genesis of ulcer. This study was therefore undertaken to evaluate the relative importance of pepsin in the causation and the therapy of ulcer. Our objective was to determine whether inactivation of pepsin, rather than alteration of gastric acidity, would permit healing of the ulcer in a patient with gastroduodenal ulcerative disease. To achieve this goal we investigated the possible pepsin-inhibitory action of (1) the various therapeutic agents used in the treatment of patients with ulcer and (2) other compounds whose therapeutic value had not yet been investigated but which appeared promising.

IN VITRO EXPERIMENTS

For the determination of pepsin we used a slightly modified Anson-Mirsky method [2] which was satisfactory in that the substrate used was reproducible and the results could be readily duplicated. This technic made it possible to demonstrate that the therapeutic agents customarily used in the therapy of ulcer inhibit "peptic" activity only through change of the hydrogen ion concentration and not by direct action on pepsin.[3]

These results, confirmed by Kirsner and co-workers,[4] led us to our next objective. This was to find a nontoxic material which would inactivate pepsin without altering intragastric acidity in order to avoid any changes in body chemistry. Dr. H. B. Bull, of the department of physiological chemistry of the Northwestern University Medical School, had shown that sodium lauryl sulfate, a surface-active agent, would denature a protein such as egg albumin in very dilute concentrations.[5] Since pepsin is a protein we decided to investigate the surface-active agents, such as the sulfate esters of the straight chain fatty alcohols, e. g., sodium lauryl sulfate, sodium palmityl sulfate, sodium stearyl sulfate and sodium oleyl sulfate. This group of substances was found to inhibit peptic activity in dilute concentrations without altering acidity. A combination of the aforementioned four substances, sodium alkyl sulfate, was almost as effective a pepsin inhibitor as any one of these compounds used individually. Therefore, sodium alkyl sulfate was used in our further work because it combined efficacy with availability.

IN VIVO EXPERIMENTS

Wangensteen, Code and associates [6] have shown that dogs will die of gastroduodenal ulcer

From the Department of Surgery and Physiological Chemistry, Northwestern University Medical School.

1. Palmer, W. L.: The Stomach and Military Service, J. A. M. A. **119**:1155 (Aug. 8) 1942.

2. Anson, M. L., and Mirsky, A. E.: The Estimation of Pepsin with Hemoglobin, J. Gen. Physiol. **16**: 59, 1932. Anson, M. L.: Estimation of Pepsin, Trypsin, Papain and Cathepsin with Hemoglobin, ibid. **22**:79, 1938.

3. Shoch, D., and Fogelson, S. J.: Studies on Peptic Inhibition, Proc. Soc. Exper. Biol. & Med. **50**:304, 1942.

4. Warren, I. A.; Front, J., and Kirsner, J. B.: The Effect of Antacid Therapy on the Peptic Activity of Gastric Juice in Man, Gastroenterology **1**:102, 1943.

5. Bull, H. B., and Neurath, H.: The Denaturation and Hydration of Proteins: II. Surface Denaturation of Egg Albumin, J. Biol. Chem. **118**:163, 1937.

6. Walpole, S. H.; Varco, R. L.; Code, C. F., and Wangensteen, O. H.: Production of Gastric and Duodenal Ulcers in the Cat by Intramuscular Implanta-

(Footnote continued on next page)

or its complications in about thirty days if given daily injections of massive doses of histamine in a liquid petrolatum–beeswax base. Following Code's personal instructions, we were able to confirm their findings. We found the gastric secretion of these animals to have not only the high acid values reported by Wangensteen but also marked peptic activity.

The next study was to determine the effect of altering this gastric secretion so that the elevated acid component remained but the pepsin was inactivated. Another group of dogs was given daily injections of massive histamine doses but were fed in addition ten 0.1 Gm. capsules of sodium alkyl sulfate at hourly intervals every day. The addition of the sodium alkyl sulfate was found to inactivate the pepsin during the twelve hour observation period without changing the high gastric acidity. The survival time of this series of dogs was prolonged to well over two hundred days in approximately half the animals.[7]

DETERMINATION OF A NONTOXIC DOSAGE OF SODIUM ALKYL SULFATE

Since surface-active agents, such as sodium alkyl sulfate, are believed to be toxic[8] and are able to denature not only pepsin but also trypsin and other proteins,[9] we fed 15 kilogram dogs 2 Gm. of sodium alkyl sulfate per day and after ten months found no alteration in the red blood cell count, the white blood cell count, the hemoglobin, the blood proteins or the urine and no loss in body weight. Sections of liver and kidney from dogs which had been treated for seven months were normal. One of us (S. J. F.) took 1 Gm. of sodium alkyl sulfate daily for eight weeks without toxic effect. These negative results plus the results of additional studies on rats and rabbits by Dr. R. K. Richards, of the Abbott Laboratories, demonstrated that sodium alkyl sulfate was probably not toxic in the doses used by us.

CLINICAL OBSERVATIONS

A clinical study was undertaken on patients whose ulcers were considered intractable because the symptoms could not be controlled by any known therapy. Some of these patients had undergone one or more gastric resections. The quantity of sodium alkyl sulfate administered was governed by two factors. Our first objective was to inactivate the pepsin of the gastric secretion, and our second, to avoid toxic effects.

Study of the Wangensteen dogs, which are marked hypersecretors of a highly acid gastric juice rich in pepsin, demonstrated that 0.1 Gm. of sodium alkyl sulfate would inactivate all the pepsin secreted in one hour. The human patient secretes more pepsin than the dog. This dose did not inactivate all the pepsin in the patient with ulcer but was used because clinical trial demonstrated freedom from toxicity.

Added experience has shown that a routine consisting of 0.2 Gm. of sodium alkyl sulfate followed in an hour by 3 ounces (84 cc.) of a milk and cream mixture gives better results.

Sodium alkyl sulfate should be administered alone because Kirsner and co-workers[10] have shown that the phospholipids contained in milk and other foods have an inhibitory effect on the pepsin-inactivating power of sodium alkyl sulfate. All antacids were omitted. Pain or pyrosis was controlled by gastric aspiration. When the subjective symptoms were controlled, the dietary regimen was supplemented with the customary high caloric, high vitamin ulcer diet, containing liberal portions of bland, smooth bulk or pureed vegetables. Constipation, if present, was treated by enema as indicated.

Results.—In a series of 34 patients with ulcer considered intractable because it did not respond to previous therapy, including surgical intervention in 5 instances, there were 26 satisfactory results and 8 failures following sodium alkyl sulfate therapy. In most of the patients responding to sodium alkyl sulfate there was marked improvement within ten days, although no result was classified as a failure until the treatment had been given a thirty day trial.

REPORT OF CASES

CASE 1.—The first patient treated was 40 years old when admitted to the Cook County Hospital in August

tion of Histamine, Proc. Soc. Exper. Biol. & Med. **44**:619, 1940. Varco, R. L.; Code, C. F.; Walpole, S. H., and Wangensteen, O. H.: Duodenal Ulcer Formation in the Dog by Intramuscular Injections of a Histamine Beeswax Mixture, Am. J. Physiol. **133**:475, 1941.

7. Shoch, D., and Fogelson, S. J.: The Effect of a Protein Denaturant on Histamine Ulcers, Quart. Bull., Northwestern Univ. M. School **16**:142, 1942.

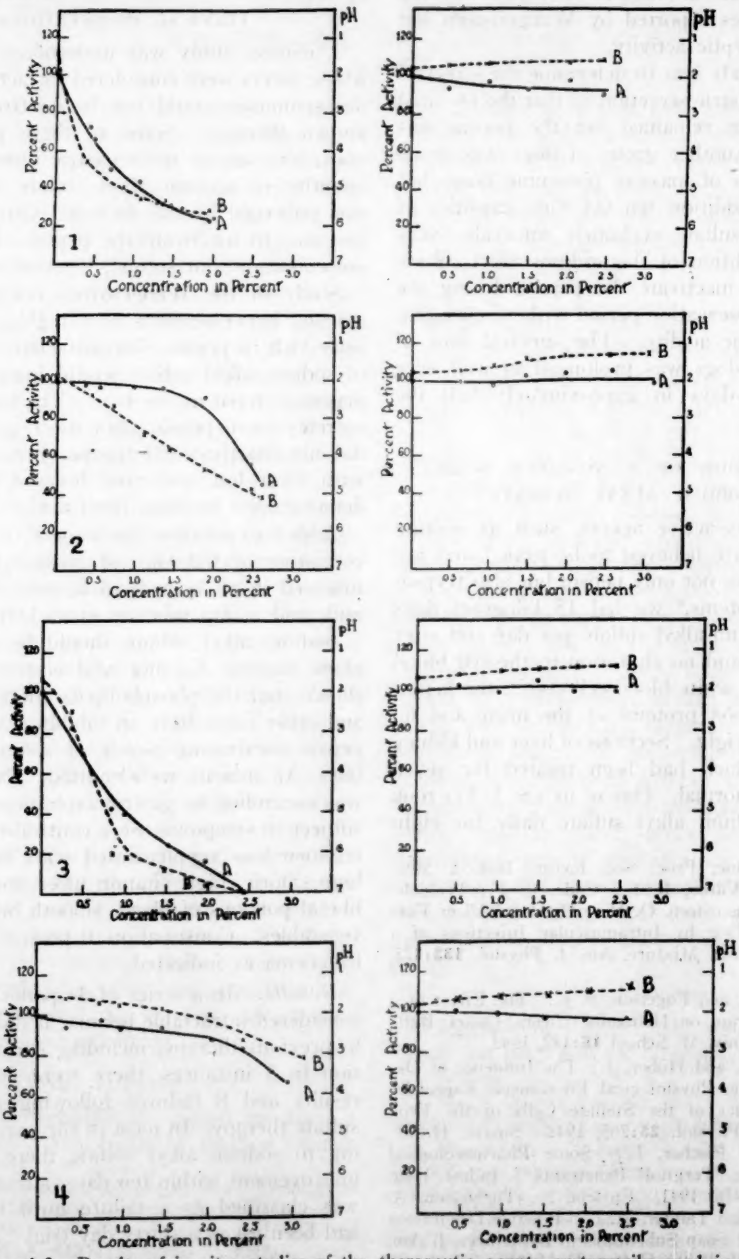
8. Höber, R., and Höber, J.: The Influence of Detergents on Some Physiological Phenomena, Especially on the Properties of the Stellate Cells of the Frog Liver, J. Gen. Physiol. **25**:705, 1942. Smyth, H. F.; Seaton, J., and Fischer, L.: Some Pharmacological Properties of the "Tergitol" Penetrants, J. Indust. Hyg. & Toxicol. **23**:478, 1941. Epstein, S.; Throndson, A. H.; Dock, W., and Tainter, M. L.: Possible Deleterious Effects of Using Soap Substitutes in Dentrifices, J. Am. Dent. A. **26**:1461, 1939. Hatton, E. H.; Fosdick, L. S., and Calandra, J.: The Toxicity and Rubefacient Action of Sulfated Higher Alcohols, J. Dent. Research **19**:87, 1940.

9. Anson, M. L.: The Denaturation of Proteins by Synthetic Detergents and Bile Salts, J. Gen. Physiol. **23**:239, 1939.

10. Kirsner, J. B.: Personal communication to the authors.

1939. He had experienced "indigestion" for ten years. A diagnosis of duodenal ulcer was made. A medical management with alkaline powders and frequent meals was started, and he was placed in a convalescent home where he remained until April 1940. He was then readmitted to the hospital for additional therapy because his ulcer was still active.

In May 1940 a stenosing duodenal ulcer was found by surgical exploration and a partial gastric resection was done with a posterior end to side anastomosis. He was returned to the convalescent home and kept under medical management. Despite this, symptoms recurred. In April 1941 severe gastric hemorrhage necessitated rehospitalization. At this time a diagnosis of marginal



Charts 1, 2 and 3.—Results of in vitro studies of the therapeutic agents customarily used in the therapy of gastric ulcer: aluminum hydroxide (*1*), aluminum phosphate (*2*) and magnesium trisilicate (*3*). In all the charts line A represents the activity of pepsin and line B the p_H. The graphs shown at the left represent the result when the agent was unbuffered; those at the right, the result when the agent was buffered. All three sets of charts show that increasing concentration of the agent decreases peptic activity only when the agent is unbuffered.

Chart 4.—Increasing concentration of gastric mucin decreases peptic activity only when the gastric mucin is unbuffered.

ulcer was confirmed by roentgenogram. A radical subtotal resection was done in July. The patient returned to the convalescent home, where he was kept under ulcer management. His symptoms recurred in two months and could not be controlled despite strict adherence to the antacid routine at the sanatorium.

He was readmitted to the Cook County Hospital in April 1942, where the diagnosis of marginal ulcer was confirmed by gastroscopic examination. The alkaline powders were replaced by 0.1 Gm. of sodium alkyl sulfate on the half hour with a milk and cream mixture on the hour. On April 15, after two weeks of sodium alkyl sulfate therapy, the patient had practically no pain, and gastroscopic examination showed the ulcer to be 50 per cent smaller, which explained the subjective improvement. On April 29 the stoma could not be visualized, but the gastric mucosa "was normal in color instead of being fiery red as seen on the last visualization." May 6, after slightly over one month's therapy with sodium alkyl sulfate, the gastroscopic report was, ". . . no ulceration was seen, there was no edema and acute inflammation had entirely left the stomach." On May 20 the gastroscopic report was, ". . . no ulceration was seen, and the mucous membrane was apparently intact throughout. The rugal markings were a little more red than normal and apparently slightly edematous." Opinion: "A normal gastric stump with a moderate amount of acute superficial gastritis."

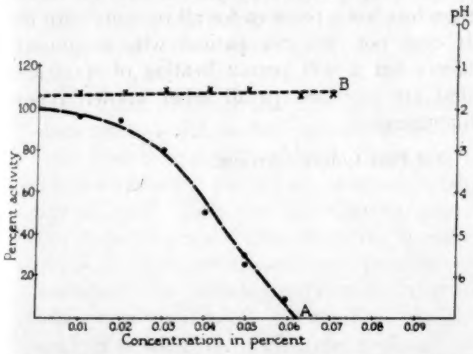


Chart 5.—Sodium alkyl sulfate decreases peptic activity without any alteration in p_H. Note effectiveness of dilute concentrations. *A* represents activity of pepsin; *B*, p_H.

This patient was discharged May 22, 1942, well enough to leave a hospital or a convalescent home for the first time in two and one-half years. He immediately took a ten hour a day job in a foundry and despite warning stopped both medication and diet. By November he again had symptoms of ulcer which required hospitalization. Another marginal ulcer was visualized but responded to treatment with sodium alkyl sulfate. On March 8, 1943 this man was symptom free and self supporting.

CASE 29.—A diagnosis of duodenal ulcer was made in 1931 in regard to a 49 year old man. He tried almost every known therapy for the ulcer without relief until 1941, when gastroenterostomy was done. This afforded no relief, and he was a patient either in the Northwestern University Medical School Clinic or the Wesley Memorial Hospital for one year. During this time varied orthodox routines were tried. He adhered faithfully to the prescribed regimens without relief. On June 6, 1942, gastroscopic examination demonstrated a lesser curvature, prepyloric and a gastrojejunal ulcer, each about 2½ inches (6 cm.) in diameter. The sodium alkyl sulfate routine was started, with marked diminution of subjective symptoms within four days. On June 30 gastroscopic study revealed almost complete healing of both ulcers. He was discharged from the hospital July 25. During his stay in the hospital the routine laboratory findings remained unchanged except the icteric index, which on June 25 was 12.5. Subsequently it returned to 5.3, where it remained.

November 9 he reentered the hospital, complaining of vomiting with complete absence of pain. November 10 the gastroscopic report indicated complete healing of the gastric and stomal lesions. A gastric resection was done then, and the pathologist's report was, ". . . no break in the mucosa, some injection and some hemorrhage in the mucosa with perivascular and lymphatic infiltration."

These two large ulcers had healed, and they remained healed, despite obstruction, while the patient followed the sodium alkyl sulfate routine.

COMMENT

The role of pepsin in the formation of ulcer may now be reevaluated. Our studies have shown that the antacids customarily used clinically in the management of patients with ulcer inhibit peptic activity indirectly through change in gastric acidity. Dogs given daily injections of massive doses of histamine and fed sodium alkyl sulfate showed no change in gastric acidity, only inactivation of pepsin. These animals exhibited marked prolongation of survival time as contrasted with a similar series of animals not treated with sodium alkyl sulfate. In addition, healing was visualized by gastroscope in patients not responding to any other medication, including 2 patients who had undergone extensive gastric resections. Another patient, with an active gastrojejunal ulcer, was treated with sodium alkyl sulfate. He subsequently required gastric resection for obstruction. The resected specimen demonstrated histologic evidence of healing of the ulcer.

All this suggests reevaluation of the destructive factors in the genesis of ulcer.

From these studies, may we not consider the possibility that the satisfactory clinical results obtained with antacids have been achieved by indirect inactivation of pepsin through change of the hydrogen ion concentration rather than by neutralization of gastric acidity per se?

Acid is important. Without acid there is no ulcer. But without acid there is no peptic activity. The advantage of the routine suggested by us permits inhibition of peptic activity with a minimum of disturbance to body chemistry.

Research with surface-active agents has enabled us to separate the effect of peptic digestion from acid erosion. This has given encouraging results which will be further pursued in the attempt to clarify the enigma of ulcer and possibly afford a new and effective rationale of therapy for

ulcers that are resistant to orthodox management. At present, this clinical research is in its infancy. Further clinical experience has shown that the dosage may be safely increased two or three fold, although an occasional patient finds sodium alkyl sulfate irritating.

We are in complete accordance with Winkelstein,[11] who expects that "a new ulcer therapy should demonstrate (1) that it is rational, (2) that it is practical and (3) that it produces prompt and more persistent results than other forms of therapy." We add the stipulation, however, that a new form of ulcer therapy must heal ulcers which have not responded to the other types of therapy. The Abbott Laboratories are cooperating in supplying us with sufficient material so that sodium alkyl sulfate is being distributed to clinicians who will assist in its therapeutic evaluation. The product will be released to members of the medical profession only if it continues to demonstrate merit.

SUMMARY AND CONCLUSIONS

Sodium alkyl sulfate, a surface-active agent, was well tolerated by patients who were given 0.2 Gm. every two hours throughout the day. No toxic effects occurred in either the experimental animal or man in the course of seven months' administration of this dose.

The survival time of dogs treated according to the Wangensteen technic with massive daily doses of histamine was markedly prolonged by the oral administration of sodium alkyl sulfate, which inactivated the pepsin in the stomach and did not alter the acidity.

All patients sent to us for clinical trial of sodium alkyl sulfate were classified as having "intractable" ulcer by their physicians because their symptoms could not be controlled by any orthodox management, including surgical therapy in 6. Twenty-six of 34 patients with gastroduodenal ulcerative disease had their symptoms controlled by sodium alkyl sulfate and were physically restored so that they were accepted by either the armed forces or industry.

Eight patients obtained no relief from this therapy. Two have already had recurrences on cessation of medication despite definite healing of the original lesions. Sodium alkyl sulfate is therefore not a panacea for all patients with ulcer. It does not cure the patient who is subject to ulcers but it will permit healing of some ulcers that are resistant to all other known types of management.

303 East Chicago Avenue.

11. Winkelstein, A.; Cornell, A., and Hollander, F.: Intragastric Drip Therapy for Peptic Ulcer, J. A. M. A. **120**:743 (Nov. 7) 1942.

PRIMARY ATYPICAL PNEUMONIA

AN ANALYSIS OF SEVEN HUNDRED AND THIRTY-EIGHT CASES OCCURRING DURING 1942 AT SCOTT FIELD, ILL.

CAPTAIN CHARLES A. OWEN
MEDICAL CORPS, ARMY OF THE UNITED STATES

Primary atypical pneumonia as a clinical entity has only recently received prominent attention. It is usually a mild disease, differing widely from the classic lobar and bronchial pneumonias; it is communicable, has a prolonged period of incubation and is prone to occur in military camps, schools and other groups with frequent intimate contacts. It is a nonbacterial disease. It is characterized by insidious onset, coughing and progressive malaise; there is usually a brief febrile period during which the pulse and the respiration are relatively slow and there is a relative or absolute leukopenia, with minimal early signs of pneumonia but with the rales persisting after the roentgenogram appears normal.

There is little evidence that this is a new disease since reports of a similar pneumonia extend back into the nineteenth century. Stansfield,[1] in 1923, discussed the pulmonary involvement in 12 cases of grip. Cole and MacCallum,[2] summarizing data on pneumonias occurring in military camps in 1918, mentioned one type of bronchopneumonia with pathologic changes similar to those of primary atypical pneumonia. Leichtenstern,[3] reviewing the influenza epidemic of 1889, likewise commented on certain pneumonic complications unlike those in the majority of cases of influenzal pneumonia. Delafield,[4] in 1884, described a "rare" subacute bronchopneumonia of adults. Interstitial pneumonia has been detected in preserved lungs of soldiers of the Civil War, and pneumonia following measles in the War of 1812 has been mentioned.[5] All these in certain respects resemble the current form of atypical pneumonia.

However, the increasing occurrence of atypical pneumonia in the past few years cannot be attributed solely to increased recognition. In reports covering periods of several years, Bowen[6] in Hawaii, Miller and Hayes[7] at the University of Oregon, Smiley, Showacre, Lee and Ferris[8] at Cornell University, Murray[9] at Harvard University, McKinlay and Cowan[10] at the University of Minnesota, Gallagher[11] and Goodrich and Bradford[12] have described a steadily increasing incidence of this disease.

The majority of cases have been reported from military establishments. Bowen[6] in 1935 described 120 cases in the armed forces at Hawaii, and Allen[13] at Fort Sam Houston, Texas, gave impetus to its recognition. Over 1,750 cases have so far been reported from these military posts and from those in Louisiana,[14] Texas,[15]

1. Stansfield, O. H.: A Pulmonary Sequel of Influenza, Boston M. & S. J. **188**:734 (May 10) 1923.

2. Cole, R., and MacCallum, W. G.: Pneumonia at a Base Hospital, J. A. M. A. **70**:1146-1156 (April 20) 1918.

3. Leichtenstern, O.: Influenza und Dengue, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1896, vol. 4, pt. 1, pp. 1-222.

4. Delafield, F.: The Pathology of Broncho-Pneumonia, Boston M. & S. J. **111**:484-487, 1884.

5. Wall, J. S.: Interstitial Bronchopneumonia in Children, South. M. J. **30**:201-206 (Feb.) 1937.

6. Bowen, A.: Acute Influenza Pneumonitis, Am. J. Roentgenol. **34**:168-174 (Aug.) 1935.

7. Miller, F. N., and Hayes, M. G.: Bronchopneumonia of Mild Severity at University of Oregon, Northwest Med. **38**:12-14 (Jan.) 1939.

8. Smiley, D. F.; Showacre, E. C.; Lee, W. F., and Ferris, H. W.: Acute Interstitial Pneumonitis: A New Disease Entity, J. A. M. A. **112**:1901-1904 (May 13) 1939.

9. Murray, M. E.: Atypical Bronchopneumonia of Unknown Etiology, Possibly Due to a Filterable Virus, New England J. Med. **222**:565-573 (April 4) 1940.

10. McKinlay, C. A., and Cowan, D. W.: Acute Respiratory Infections Including Lobar Pneumonia and Atypical Pneumonia in a Young Adult Group, Journal-Lancet **61**:125-133 (April) 1941.

11. Gallagher, J. R.: Acute Pneumonitis: Report of an Epidemic, Yale J. Biol. & Med. **13**:769-781 (July) 1941.

12. Goodrich, B. E., and Bradford, H. A.: The Recognition of Virus Type Pneumonia, Am. J. M. Sc. **204**:163-179 (Aug.) 1942.

13. Allen, W. H.: Acute Pneumonitis, Ann. Int. Med. **10**:441-446 (Oct.) 1936.

14. (*a*) Moore, G. B.; Tannenbaum, A. J., and Smaha, T. G.: Atypical Pneumonia in an Army Camp, War Med. **2**:615-622 (July) 1942. (*b*) Dingle, J. H., and others: Primary Atypical Pneumonia, Etiology Unknown, ibid. **3**:223-248 (March) 1943. (*c*) McCarthy, P. V.: Primary Atypical Pneumonia of Unknown Etiology, Radiology **40**:344-346 (April) 1943.

15. Duggan, L. B., and Powers, W. L.: An Acute Respiratory Infection Resembling So-Called Acute Pneumonitis, U. S. Nav. M. Bull. **40**:651-659 (July) 1942.

Florida,[16] California,[17] Canada,[18] North Carolina[19] and Panama.[20] Only 5 deaths have been mentioned, an incidence of 0.3 per cent.

Studies of over 1,100 cases from civilian sources have been published. Several of the early reports were from England[21]; in this country atypical pneumonia has been described in New York,[22] Massachusetts,[23] New Jersey,[24] Washington, D. C.,[25] Maryland,[26] Pennsylvania,[27] Virginia,[28] North Carolina,[29] Ohio,[30] Michigan,[12] Minnesota,[31] Illinois,[32] Oklahoma,[33] Texas,[34] California[35] and Oregon.[31c] In general these cases seem to be more severe, with 26 deaths reported (2.4 per cent). This is not unexpected, as the patients with the milder attacks of the disease either are not seen by physicians or are treated at home.

The nomenclature of this disease has become confused because of the uncertain etiology. Etiologic terms such as "acute influenza pneumonitis," [6] "influenzal pneumonitis" [33] and "primary virus pneumonitis" [31e] lack laboratory confirmation. "Disseminated focal pneumonia" [21b] has been proposed on the basis of the roentgenographic appearance; "atypical pneumonia with leukopenia" [34] emphasizes a laboratory finding; "acute interstitial pneumonitis" [8] reflects the microscopic appearance. Such terms as "pneumonitis" or "acute pneumonitis" [13] do not seem sufficiently limiting. At present the most popular names indicate the uncertain etiology: "atypical pneumonia," [23b] "atypical bronchopneumonia," [9] "bronchopneumonia of unknown etiology," [36] or the official military diagnosis,

16. Green, D. M., and Eldridge, F. G.: Primary Atypical Pneumonia, Etiology Unknown, Mil. Surgeon **91**:503-517 (Nov.) 1942.

17. Whitely, J. H.; Bernstein, A., and Goldman, M.: Primary Atypical Pneumonia—A Report of Twenty-Five Cases, Mil. Surgeon **91**:499-502 (Nov.) 1942.

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19. Curtzwiler, M. C., and Moore, B. E.: Primary Atypical Pneumonia of Unknown Etiology, Radiology **40**:347-350 (April) 1943.

20. Campbell, E. T.: Primary Atypical Pneumonia and Malaria, War Med. **3**:249-255 (March) 1943.

21. (*a*) Scadding, J. G.: Lung Changes in Influenza, Quart. J. Med. **6**:425-465 (Oct.) 1937; (*b*) Disseminated Focal Pneumonia, Brit. M. J. **2**:956-959 (Nov. 13) 1937. (*c*) Gill, A. M.: Pneumonitis, ibid. **1**:504-507 (March 5) 1938. (*d*) Maxwell, J.: Pneumonitis, Lancet **2**:239-241 (July 30) 1938. (*e*) Ramsay, H., and Scadding, J. G.: Benign Broncho-Pulmonary Inflammations Associated with Transient Radiographic Shadows, Quart. J. Med. **8**:79-95 (April) 1939.

22. (*a*) Kneeland, Y., Jr., and Smetana, H. F.: Current Broncho-Pneumonia of Unusual Character and Undetermined Etiology, Bull. Johns Hopkins Hosp. **67**: 229-267 (Oct.) 1940. (*b*) Smiley, Showacre, Lee and Ferris.[8]

23. (*a*) Gallagher, J. R.: Bronchopneumonia in Adolescence, Yale J. Biol. & Med. **7**:23-40 (Oct.) 1934. (*b*) Cass, J. W.: The Question of "Influenza" and Atypical Pneumonia, New England J. Med. **214**: 187-193 (Jan. 30) 1936. (*c*) Bock, A. V.: Clinical Observations, Complications and Treatment of Acute Upper Respiratory Tract Infections, Ann. Int. Med. **12**:317-322 (Sept.) 1938. (*d*) Gallagher, J. R.: Acute Pneumonitis: A Report of Eighty-Seven Cases Among Adolescents, Yale J. Biol. & Med. **13**:663-678 (May) 1941. (*e*) Favour, C. B.: Ornithosis (Psittacosis): A Report of Three Cases and a Historical, Clinical, and Laboratory Comparison with Human Atypical (Virus) Pneumonia, Am. J. M. Sc. **205**:162-187 (Feb.) 1943. (*f*) Murray.[9] (*g*) Gallagher.[11]

24. Rainey, W. G., and Burbridge, J. R.: Acute Pneumonitis or Atypical Pneumonia, Journal-Lancet **59**:101-104 (March) 1939.

25. Hornibrook, J. W., and Nelson, K. R.: An Institutional Outbreak of Pneumonitis: I. Epidemiological and Clinical Studies, Pub. Health Rep. **55**:1936-1944 (Oct. 25) 1940.

26. Longcope, W. T.: (*a*) Bronchopneumonia of Unknown Etiology (Variety ×): A Report of Thirty-Two Cases with Two Deaths, Bull. Johns Hopkins Hosp. **67**:268-305 (Oct.) 1940; (*b*) Pneumonitis or Virus Pneumonia, Practitioner **148**:1-8 (Jan.) 1942.

27. (*a*) Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia, J. A. M. A. **111**:2377-2384 (Dec. 24) 1938. (*b*) Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract, Arch. Int. Med. **65**:138-150 (Jan.) 1940.

28. Daniels, W. B.: Bronchopneumonia of Unknown Etiology in a Girls' School, Am. J. M. Sc. **203**:263-276 (Feb.) 1942.

29. Moss, J.: Some Features of "Virus Pneumonia," North Carolina M. J. **3**:27-30 (Jan.) 1942.

30. Hufford, C. E., and Applebaum, A. A.: Atypical Pneumonia of Probable Virus Origin, Radiology **40**: 351-360 (April) 1943.

31. (*a*) McKinlay, C. A.: Acute Diffuse Bronchiolitis with Report of Case, Journal-Lancet **59**:90-91 (March) 1939. (*b*) Adams, J. M.: Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies: Study of an Epidemic Involving Thirty-Two Infants, with Nine Deaths, J. A. M. A. **116**:925-933 (March 8) 1941. (*c*) Adams, J. M.; Green, R. G.; Evans, C. A., and Beach, N.: Primary Virus Pneumonitis, J. Pediat. **20**: 405-420 (April) 1942. (*d*) McKinlay and Cowan.[10]

32. Rhoads, P. S.: The Probable Incidence and Clinical Features of "Virus" Pneumonia, Radiology **40**: 327-338 (April) 1943.

33. Ackermann, A. J.: Roentgenological Considerations of Influenzal Pneumonitis, Am. J. Roentgenol. **46**:175-181 (Aug.) 1941.

34. Maxfield, J. R.: Atypical Pneumonia with Leukopenia, Texas State J. Med. **35**:340-346 (Sept.) 1939.

35. (*a*) Eaton, M. D.; Beck, M. D., and Pearson, H. E.: A Virus from Cases of Atypical Pneumonia: Relation to the Viruses of Meningopneumonitis and Psittacosis, J. Exper. Med. **73**:641-653 (May) 1941. (*b*) Eaton, M. D.; Martin, W. P., and Beck, M. D.: The Antigenic Relationship of the Viruses of Meningopneumonitis and Lymphogranuloma Venereum, ibid. **75**:21-33 (Jan.) 1942.

36. Longcope.[26a] Kneeland and Smetana.[22a]

"primary atypical pneumonia, etiology unknown." [37]

In 1942, at the Station Hospital, Scott Field, 799 patients were treated for pneumonia. Twenty-four had typical lobar pneumonia; 775, bronchopneumonia. Among the latter were 738 patients with clinical and laboratory findings suggestive of a nonbacterial cause. The remaining 37 patients suffered from the more widely recognized types of primary or secondary bacterial bronchopneumonia. The atypical pneumonia varied from that observed in a few critically ill patients to the milder forms which seemed no more serious than the ordinary "cold." Hospitalization varied from a few days to several months, and there was a distinct seasonal variation. Yet clinically this whole group exhibited sufficiently uniform signs and symptoms to be classed together as having primary atypical pneumonia.

TABLE 1.—*Types of Onset of Atypical Pneumonia (Seven Hundred and One Cases)*

	Cases
Asymptomatic onset: Patients admitted because routine roentgen films revealed pulmonary cloudiness	6
Onset with cough	247
Cough, gradual development of malaise, finally fever	214
Cough and pleuritic pain	20
Cough without other symptoms	13
Abrupt onset	260
Sudden malaise and coughing	175
Malaise initially, cough soon following	55
Malaise initially, cough late if at all	30
Onset with coryzal symptoms	122
Miscellaneous	66
Predominant symptom:	
Sore throat, mild pharyngeal injection	32
Sore throat, acute follicular tonsillitis	8
Laryngitis	9
Malaise following typhoid vaccinations	9
Nausea, vomiting and/or diarrhea	8

CLINICAL FINDINGS IN THE SEVEN HUNDRED AND THIRTY-EIGHT CASES OCCURRING IN 1942

Type of Onset.—The explosive onset of pneumococcic lobar pneumonia was rarely seen in the atypical disease. A characteristic history (table 1) was as follows: There had been bouts of coughing for several days; the patient began to feel tired and weak; there was intermittent chilliness, as well as fever and diaphoresis. True rigors were not present in any of these cases. Early the cough was nonproductive; the paroxysms often occurred following a change in position, especially during the night and on awakening in the morning. Pleuritic pain was rare, but substernal aching with coughing or deep breathing was almost the rule.

On the other hand, symptoms at times developed rapidly, though rarely in less than one to two days. In these cases malaise, aching, chilliness and fever heralded the illness, with cough following in from one to four days. In 1 patient cough was never present. Hence the diagnosis was occasionally established prior to the presence of pulmonary symptoms.

The third large group of patients had symptoms indistinguishable from those of coryza: sneezing, nasal discharge, pharyngeal irritation with associated cough and mild discomfort.

Analysis of the types of onset showed a definite seasonal variation (table 2). During the summer months the onset was more abrupt and as a rule the course was milder, requiring shorter hospitalization. During the winter the gradual onset with cough or mild coryzal symptoms predominated.

Interval Between Admission to Hospital and Diagnosis of Pneumonia.—Early findings in atypical pneumonia were usually not prominent but were sufficiently clear to enable the diagnosis to be made within the first twenty-four hours in 57 per cent of the cases; however, 9 per cent were not correctly diagnosed within the first week. In certain cases pneumonia was suspected for the first time when an apparently simple respiratory infection did not subside rapidly. In others it was masked by conditions such as asthma or measles. Further, there was always the question of cross infection in the wards.

Findings in Chest.—The most consistent single finding was moist rales. However, other changes alone or in combination were often present (table 3). In almost half the cases the chest revealed nothing unusual on admission examination, but in all but 49 it did subsequently disclose physical findings (table 4).

TABLE 2.—*Monthly Variation in Incidence of Types of Onset of Atypical Pneumonia*

1942	Abrupt Onset	Cough	Coryza
January	10	14	3
February	7	6	6
March	6	13	5
April	15	23	3
May	6	10	3
June	15	15	5
July	46	33	9
August	38	26	17
September	35	14	16
October	39	29	20
November	25	27	20
December	18	37	15

The rales usually heard early in atypical pneumonia were fine "sticky" crepitations, occurring in showers at the end of fairly deep inspirations and accentuated by coughing. As the disease

37. Primary Atypical Pneumonia, Etiology Unknown, editorial, War Med. **2**:330-333 (March) 1942.

progressed, the rales became louder and coarser and were heard during a greater portion of the inspiratory phase and later during the complete respiratory cycle. It was during this stage that dulness, diminished breath sounds and decreased fremitus were sometimes evident. At times the coarse rales faded promptly, but often they persisted after the roentgenographic changes had disappeared and the patient was well along in his convalescence. At times the rales changed to a variety of rhonchi before disappearing. Dingle and his associates [14b] have graphed the relationship of the chest findings to the roentgen appearance, indicating that the roentgenogram detects pneumonic changes earlier and clears more rapidly than is suggested by the clinical findings. Duggan and Powers [15] also emphasized the persistence of rales.

TABLE 3.—*Thoracic Findings on Admission to Hospital (Seven Hundred and Thirty-Four Cases)*

	Cases	Per Cent
Chest clear	327	45
Moist rales	274	37
Rough breath sounds	64	8.7
Rhonchi	39	5.2
Dulness	20	2.7
Friction rub	8	1.1
Increased breath sounds	2	0.3

When pulmonary disease was apparent, the involved lobe or lobes were usually readily identified. Rales heard posteriorly suggested lesions of the lower lobe and those heard anteriorly lesions of the upper lobe. When no signs in the chest were noted, the patient occasionally indicated the site of involvement by complaints of "fulness" or "aching" in one side of his chest.

TABLE 4.—*Summary of All Thoracic Evidences of Disease Observed During Hospitalization (Seven Hundred and Thirty-Four Cases)*

	Cases	Per Cent
Moist rales	548	75
Fine	469	64
Coarse	160	22
Roughened breath sounds	191	26
Dulness	163	22
Rhonchi	103	14
Bronchial breathing	52	7.1
Diminished fremitus	32	4.4
Friction rub	13	1.8
Flatness (without effusion)	5	0.7
Whispered pectoriloquy	4	0.6
No findings	49	6.7

Also, there was often a history of increased discomfort or uncontrollable coughing when lying on the affected side.

Relation of Findings in Chest to Severity of Illness.—One of the most atypical features of this pneumonia was the complete dissociation between the findings in the chest and the extent of the patient's symptoms, disability, fever and other complaints or between either of these factors and the roentgenographic appearance of pulmonary cloudiness. There might be an apparently clear chest, very slight haziness on the roentgen film, yet an acutely ill patient. On the other hand, loud rales may have been heard widely or the roentgenogram may have shown patchy cloudiness throughout a lobe while the patient was only slightly uncomfortable. This was particularly true in cases in which roentgenograms never revealed definite pneumonia, yet the clinical course was indistinguishable from that of atypical pneumonia.

CLINICAL COURSE OF ATYPICAL PNEUMONIA

Illness Prior to Hospitalization.—Symptoms usually preceded the admission of the patient to the hospital by one to seven days, occasionally weeks when a chronic cough would not "break."

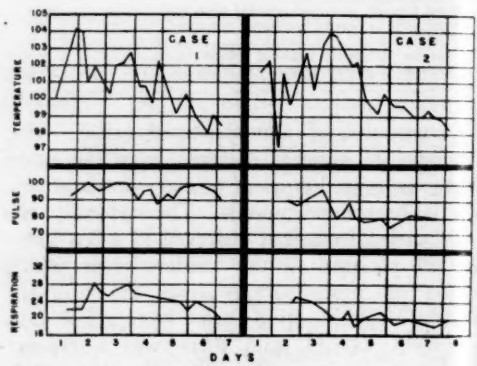

Fig. 1.—The usual febrile course as seen in 2 patients with atypical pneumonia. The pulse and respiratory rates are relatively low.

That acute symptoms of weakness, aching and fever infrequently persisted over twenty-four hours is indicated in the fact that the intensive schooling the men received demanded full mental and physical faculties. The length of the illness prior to hospitalization in the winter (six to eight days) was practically double that of midsummer (three to five).

Duration of Illness.—The average period of hospitalization was twenty-seven days, varying from twenty in summer to twenty-nine in early winter. Of this total, patients were acutely ill an average of only three and four-tenths days (two and one-tenth days in summer; four and nine-tenths days in winter).

Fever.—In atypical pneumonia, unlike the common infections of the respiratory tract, fever was seldom at the peak on admission but frequently was at the peak within the first forty-

eight hours. Temperatures ranged from normal throughout hospitalization to 106.6 F. The average peak for all cases was 102.8 F. The duration of temperatures over 100 F. averaged five days; that of temperatures over 99 F. seven and five-tenths days (figs. 1 and 2).

Patients with high fever were quite uncomfortable, especially if there was associated uncontrollable coughing. However, there was no comparison between a patient having atypical pneumonia with a temperature of 104 F. and a similar patient with lobar pneumonia. The former appeared flushed and ill at ease but in no acute distress, occasionally sitting up in bed to read or converse (fig. 3). Reimann [27a] has mentioned a biphasic type of fever, suggestive of virus infection, but it was not characteristic in this series.

hospitalization, was noted in 84 cases (12 per cent). The bronchoscopic findings of inflamed, readily injured mucosa by Dingle and coworkers [14b] and the pathologic findings of ulcerated bronchial mucosa explain this tussive blood-streaking.

Sore Throat; Pain.—The pharynx was often quite injected but seldom actually red as in exudative pharyngitis. However, Green and Eldridge [16] stated that red, congested, swollen throats were almost invariably present, and Reimann and Havens [27b] noted that 92 per cent of their series had inflamed mucous membranes.

The characteristic dry and hacking cough often caused: a "raw throat"; "burning" tracheitis; marked substernal aching; pain along the rib margins; pain and occasionally tenderness with slight rigidity of the abdominal muscles, usually

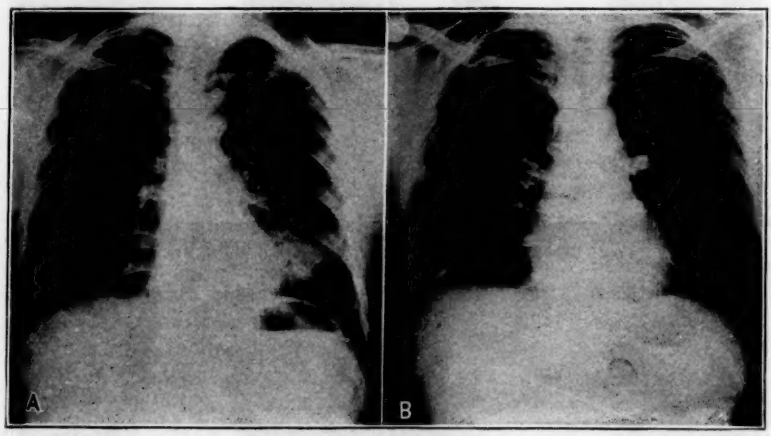

Fig. 2.—*A*, roentgenogram of the chest in case 1 on the second hospital day. This illustrates the classic cloudy mottling projecting from the hilar region.

B, roentgenogram of the chest in case 2 on the second hospital day. An unusual form of atypical pneumonia with accentuation of the bronchovascular markings extending into the right costophrenic angle.

Pulse and Respiratory Rates.—The pulse and the respiration were typhoidal: The pulse was full but not rapid; the respiration, deepened but not accelerated. The pulse rate was usually a more accurate guide than the temperature to the extent of pulmonary disease, as a rising pulse rate suggested spreading pneumonia (fig. 4), and a slow pulse in the face of a high, persistent fever indicated little cause for alarm. Seriously ill patients with rapid respiration were usually benefited by oxygen even though cyanosis and dyspnea were absent.

Hemoptysis.—In 2 cases there was copious hemoptysis of bright red blood. In neither was the cause detected, and there was complete subsidence of bleeding as the disease regressed. Blood-streaked sputum, either before or during

in the epigastric region; pain along the pelvic attachments of the abdominal musculature. In 1 patient this pain in the lower part of the abdomen was interpreted as appendicitis; however, the appendix and other abdominal viscera appeared normal at operation. Green and Eldridge [16] have also reported a case in which appendectomy was performed because of the pain in the lower part of the abdomen.

Splenic Enlargement.—Longcope [26a] noted that 12 per cent of his patients had splenomegaly; however, in the present series no splenic or hepatic enlargements were detected.

Convalescence.—There was no sharp demarcation between the acute and the convalescent stage of atypical pneumonia as typified by the crisis of pneumococcic pneumonia. Rather, the

fever slowly diminished, and the cough which had been nonproductive began to "loosen" with production of tenacious clear phlegm. There remained, however, a period of debility which was difficult to explain solely on the basis of pulmonary disease. For weeks and even months the patient had little energy, tired easily and had insufficient appetite to regain the weight lost during the early stage. This probably accounts for the longer hospitalization of patients in army camps than in civilian life, as discharge from a station hospital means return to active duty. If too energetic activity was resumed prematurely, the patient at best had a mild reactivation of coughing and development of fever; a more serious consequence was an exacerbation of his pneumonia. Frequently coughing was the last symptom to disappear.

Relation of Age to Course of Illness.—Patients ranged in age from 17 to 46. Within these limits there was no definite relation of age to severity or length of illness.

LABORATORY FINDINGS

Roentgenologic Examination.—The roentgenogram is the most important aid in the diagnosis of atypical pneumonia, as it may establish early the presence and the extent of the pulmonary lesion. However, it is not the sole means of diagnosis, an altogether too prevalent belief. For example, Duggan and Powers [15] stated that "in a large majority of cases [diagnosis] could not be made by any other means."

Roentgenograms taken early reveal accentuation of the hilar bronchovascular markings on one or both sides. Hazy densities project out-

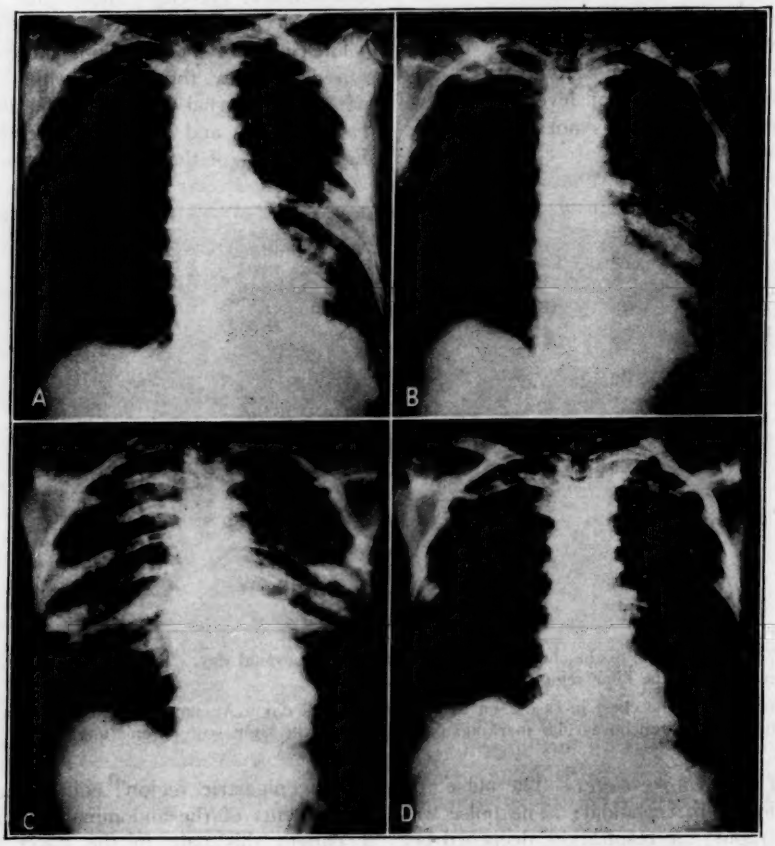

Fig. 3 (case 3).—*A*, roentgenogram of the chest taken when the patient was admitted to the hospital. Note the patchy areas of consolidation in the midportion of the lower lobe of the left lung.

B, roentgenogram of the chest on the fourth day. There is confluent mottling throughout the lower lobe and the lower portion of the upper lobe of the left lung.

C, roentgenogram of the chest on the twelfth day. All lobes are at least partially involved with the consolidations of atypical pneumonia.

D, roentgenogram of the chest on the eighteenth day. Only traces of the pneumonia remain.

ward toward the periphery of the lungs, having at first a mottled appearance, at times progressing to a more uniform cloudiness. The process may involve small portions of one lobe or may cover one or more lobes completely. With spread of the pneumonia there is again an extension from the hilar regions. Regression is not an absolute

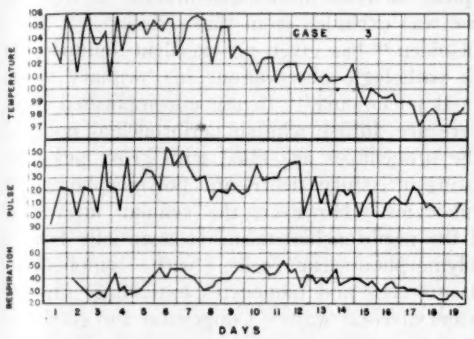

Fig. 4 (case 3).—A critically ill patient with a temperature of 105 F. for eight days. However, the pulse and respiratory rates indicate the pneumonic changes more precisely than does the temperature. Figure 3 reveals that there was steadily increasing consolidation during the first twelve days.

reversal, as the entire pneumonic area begins to fade at once, although the intensification of the bronchovascular markings is usually the last to subside. Occasionally an area of consolidation seems to enlarge slightly as its density begins to diminish.

The average duration of pulmonary consolidations in uncomplicated cases was nineteen days, as determined by serial roentgen films taken usually at seven day intervals.

Classifications of roentgenograms [38] stress the various stages of the disease, e. g., accentuation of hilar markings with projections toward the periphery, which McCarthy [14c] found to be most common, or patchy confluent areas of density, or generalized increase in pulmonary markings. The most characteristic picture is that of uneven densities, or cloudy mottling, as seen in figures 1 *A* and 3 *A* and *B*. An unusual type is characterized by peripheral areas of consolidation, sometimes suggestive of early lobar pneumonia, as in figure 2 *B*.

A predilection for involvement of a lower lobe was marked, occurring in 612 cases (83 per cent), with a slight but definite predominance of the left lower lobe (table 5). Extensions of the pneumonic process occurred in 64 cases, with extension to the opposite lung in 40.

The diagnosis of pneumonia was made in 15 cases (2 per cent) with no definite roentgen changes beyond accentuation of truncal markings; this seemed justified from the clinical course and findings. Dingle and his associates [14b] have also noted the difficulty in distinguishing between certain types of tracheobronchitis and tracheobronchopneumonia.

In 30 cases (4 per cent) the findings in the chest suggested pneumonia while the initial roentgen films appeared normal, though the later ones were confirmatory. The detection of pulmonary signs prior to roentgenographic evidence is in sharp contrast to the usual minimal findings in the early stages. In 14 cases, in which both the roentgen and the thoracic findings were negative early but subsequently positive, pneumonia was suspected on the basis of the history and the general appearance of the patient.

Studies of Sputum.—Certain roentgen films suggested a tuberculous process. Sputums from 52 patients were studied for Mycobacterium tuberculosis. In no instance were acid-fast organisms discovered.

Sputums from 275 patients were examined for the presence of Diplococcus pneumoniae. Gram-positive diplococci were found in 82 sputums, but in only 28 were type-specific pneumococci identified. Types usually considered to be significant were present in sputums from 6 patients: 1, 2, 5, 7, 9 and 11. The majority of the remaining types found were the less significant higher types. In no case were the identified organisms etiologically important from a clinical standpoint. Certain of the cases ruled out of this series were cases of bronchopneumonia with type-specific pneumococci, marked leukocytosis, tachycardia and response to chemotherapy.

TABLE 5.—*Lobes Involved in Atypical Pneumonia as Determined by Roentgenography*

	Cases
Involvement of a single lobe throughout illness	577
Left lung	317
Right lung	260
Lower lobe of left lung	289 (50%)
Lower lobe of right lung	208 (36%)
Upper lobe of right lung	32 (5.5%)
Upper lobe of left lung	28 (5.0%)
Middle lobe of right lung	20 (3.5%)
Involvement of more than one lobe on admission to the hospital	78
Lower lobes of right and left lungs	37 (47%)
Middle and lower lobes of right lung	10 (13%)
Entire left lung	9 (12%)
Entire right lung	6 (8%)
All lobes of both lungs	4 (5%)
Other combinations	12 (15%)

38. Kornblum, K., and Reimann, H. A.: The Roentgenological Aspects of an Epidemic of Acute Respiratory Tract Infection, Am. J. Roentgenol. **44**:333-344 (Sept.) 1940. Smiley, Showacre, Lee and Ferris.[8] McCarthy.[14c]

Blood Counts.—A relative leukopenia with respect to fever and severity of illness was characteristic. The average leukocyte count on admission was 9,860, although the mean value, 9,080, was more representative. The lowest count was 2,600; the highest, 30,000. The summer leukocyte counts averaged distinctly lower (9,200) than the winter ones (10,250). These figures tend to confirm the majority of reports, although Cass [23b] stated that in his series most leukocyte counts ranged from 2,500 to 4,500 (80 to 90 per cent polymorphonuclear cells), with the lower counts representing the more seriously ill patients.

Differential counts were made in only a few cases. They showed that fluctuation varied with the polymorphonuclear leukocytes and that in counts under 8,000 there were often eosinophils up to not more than 10 per cent. Longcope [26a] noted slight eosinophilia in over half of his 32 cases. However, this disease does not apparently simulate Löffler's eosinophilic pneumonia.[39]

Among patients who were critically ill, counts of 15,000 to 18,000 were common, uninfluenced by treatment with sulfonamide compounds. With convalescence the leukocytosis usually dropped parallel with clinical improvement, while low counts tended to rise to normal or slightly higher. Kneeland and Smetana [22a] and Curtzwiler and Moore [19] found moderate leukocytosis with convalescence in even the milder illnesses.

Erythrocyte counts were normal, although during convalescence hemoglobin values were often slightly depressed.

Urinalysis.—Urinalysis was performed routinely, yet in only 8 cases were abnormalities detected. Glycosuria occurred in 2 cases early in the illness and disappeared promptly. Albuminuria was observed in 4 instances, in each case at the height of the fever, and lasted from one to four days. None of the patients with these symptoms was seriously ill. Following the use of sulfonamide compounds, transient hematuria was detected in 2 patients.

Blood Cultures.—In the few instances in which blood cultures were made they were negative. This confirms the observations of Reimann [27a] and of Daniels.[28]

Serologic Tests.—The Kahn test was performed in 518 cases. In 3 cases it was transiently positive (0.6 per cent); in only 1 case was it positive as long as four weeks. Kneeland and Smetana [22a] reported a similar case.

39. Reimann, H. A.: Infectious Diseases, Arch. Int. Med. **64**:362-405 (Aug.) 1939.

PATHOLOGY

No patients with uncomplicated atypical pneumonia died. Four patients were extremely sick, and though death was felt to be imminent, all recovered. One patient, admitted with a diagnosis of atypical pneumonia, died of empyema, with the additional observation at autopsy of typical bacterial bronchopneumonia, so that the case was excluded from this series.

Golden [40] has given an excellent summary of the pathologic observations in "primary interstitial pneumonia." In the uncomplicated cases there are diffuse whitish peribronchial nodules. The bronchioles are filled with gross pus, consisting of cellular debris and polymorphonuclear leukocytes. However, the cellular infiltration of the peribronchial tissue is essentially free of polymorphonuclear cells, with lymphocytes, plasma cells and monocytes extending into adjacent alveolar walls. Congestion and edema of the lung tissue are common, again free of polymorphonuclear leukocytes and bacteria. With secondary infection, hemorrhage, polymorphonuclear leukocytes and fibrin formation become prominent but do not obscure the fundamental process. Other organs commonly show alterations: the spleen, congestion but not hyperplasia; the liver, minute foci of necrosis; the diaphragm, hyaline necrosis of muscle fibers. Golden stated that these pulmonary lesions are not pathognomonic of atypical pneumonia, as similar changes are found in other interstitial pneumonias of known causes.

Thirty-one deaths from atypical pneumonia have been reported, including 9 in the severe epidemic among infants reported by Adams and his associates.[41] The remaining 22 deaths occurred in: 7 patients who apparently were overcome by the severity of the pneumonia [42] and who had pleurisy [22a] and sterile effusions [43]; 2 with empyema caused by Streptococcus haemolyticus infection [23b]; 1 who succumbed to intercurrent lobar pneumonia [21d]; 2 who had fatal encephalitic complications [44]; 5 who had cardiac disabilities: 3 who had old rheumatic carditis [45]; 1 in whom autopsy re-

40. Golden, A.: Interstitial Pneumonitis, Army Medical Museum Study Material, January 1943.

41. Adams.[31b] Adams, Green, Evans and Beach.[31c]

42. Lillie, R. D.; Perrin, T. L., and Armstrong, C.: An Institutional Outbreak of Pneumonitis: III. Histopathology in Man and Rhesus Monkeys in the Pneumonitis Due to the Virus of "Q" Fever, Pub. Health Rep. **56**:149-155 (Jan. 24) 1941. Eaton, Beck and Pearson.[35a] Moore, Tannenbaum and Smaha.[14a] Hufford and Applebaum.[30]

43. Reimann.[27a] Green and Eldridge.[16]

44. Reimann.[27a] Scadding.[21b]

45. Longcope.[26a] Moore, Tannenbaum and Smaha.[14a]

vealed myocarditis [32] ; 1, a 79 year old patient, whose heart failed.[21d] There were pathologic reports on most of these cases, and the findings uniformly included peribronchial interstitial pneumonia. Saphir, describing postmortem observations on 2 patients, mentioned, in addition, hyaline membranes lining the pulmonary alveoli and intracytoplasmic inclusions of the bronchial epithelium.[46]

TREATMENT

No specific therapy is known for atypical pneumonia, so that treatment is entirely symptomatic. For general malaise in the present series of cases codeine seemed most efficient. Acetyl salicylic acid alone or in combination with acetophenetidin and caffeine effected prompt falls in temperature as a rule and thereby tended to relieve the generalized aching associated with fever. However, the accompanying drenching sweat was uncomfortable, and the erratic temperature curve made estimation of progress uncertain. As a result, routine use of the antipyretic drugs was discouraged. Sponge baths and alcohol rubs had a soothing as well as antipyretic effect.

Most troublesome to the patient and most difficult to control was coughing. During the early nonproductive stage no expectorant was found adequate. Codeine and various cough mixtures were routinely employed, with transient benefit at best. Proprietary cough drops, slowly dissolved in the mouth, at times reduced the "tickling" in the throat. With paroxysmic coughing benefit was occasionally obtained from "steam" inhalations.

If cyanosis or dyspnea developed, the use of an oxygen tent was of unquestioned value. Cyanosis, which was infrequent in this series, was found by Rhoads [32] in 12 of his 24 patients.

Convalescent serum or blood was not used, and blood transfusions were given in only the critical cases, so that benefit was difficult to determine. Green and Eldridge [16] noted suggestively beneficial results from the use of convalescent blood in 2 patients.

During convalescence, iron, ultraviolet rays or sunbaths, deep-breathing and graduated physical exercises were apparently helpful.

Chemotherapy. — Sulfonamide drugs were employed in 362 cases, with a sharp break in temperature following their administration in 42 (12 per cent), suggesting a favorable response. However, since the febrile period was usually brief, it was often difficult to determine whether a fall in temperature would not have occurred anyway.

Sulfanilamide was used in 73 cases, with apparent benefit in 8 per cent; sulfapyridine, in 21 cases, with no response; sulfathiazole, in 300 cases, with a seeming response in 11 per cent, and sulfadiazine in 61 cases, with abrupt improvement in 10 per cent. More than one type of the drug was used for the occasional patient. The dosage of the sulfonamide compound was almost invariably 4 Gm. initially, followed by 1 Gm. every four hours; sodium bicarbonate was occasionally added. Sulfapyridine was the most unpopular, inducing nausea and vomiting routinely. Sulfadiazine was best tolerated but only slightly more so than sulfathiazole.

The incidence of apparent response to sulfonamide compounds (12 per cent) in patients with leukocytosis on admission was no greater than the incidence of apparent response in all patients receiving sulfonamide compounds (table 6). This suggests that the elevated counts did not represent secondary bacterial invasion but actually reflected the primary pathologic process.

TABLE 6.—*Relationship of Leukocytosis to the Response to Sulfonamide Compounds*

Leukocyte Count on Admission	Patients Not Receiving Sulfonamide Compounds	Patients Receiving Sulfonamide Compounds: Total	Patients Receiving Sulfonamide Compounds: Number in Whom Chemotherapy Was Apparently Effective
12,000 to 14,950	47	50	4
15,000 to 17,950	17	22	4
18,000 to 19,950	4	8	2
20,000 and over	3	11	1
Totals.....	71	91	11 (12%)

The use of sulfonamide compounds was generally discredited, but in any patient who was severely ill or whose disease was protracted full doses were employed in an attempt to prevent or eradicate secondary infection. Statistics which seem to show a more rapid recovery in patients not treated with sulfonamide compounds [17] must be subjected to careful scrutiny inasmuch as only the patients with more severe disease are usually given chemotherapy.

Other Types of Therapy.—Uhlman mentioned "dramatic effects" from the use of roentgen radiation to the chest.[47] Goodrich and Bradford [12] injected neoarsphenamine into 3 patients without benefit. Campbell [20] in the treatment of patients

46. Saphir, O.: Pathological Changes in So-Called Atypical Pneumonia, Radiology **40**:339-343 (April) 1943.

47. Uhlman, E., in Discussion of Symposium on Atypical Pneumonia, Radiology **40**:360-361 (April) 1943.

for malaria and atypical pneumonia found the latter unaffected by quinine.

RECURRENCES

Seventeen patients with recurrent atypical pneumonia were admitted to the hospital during 1942, 2 of them for a third time. Recurrences are infrequently mentioned in the literature; for example, in Gallagher's [11] series of 87 cases seen over a seven year period there were no recurrences.

The interval between the initial disease and the recurrence varied from one to one hundred and twenty-three days, with the number of cases insufficient to establish a reliable average (mean, eighteen days). Usually the recurrent pneumonia was less severe, to judge by the duration of fever over 100 F.—four and four-tenths days as compared with five and eight-tenths days originally. This was not necessarily true in the individual case, as one of the most critically ill patients was one with recurrent pneumonia.

Ten patients had reinfection of the same pulmonary lobe, while the other 7 had recurrences in areas partially or totally different from those involved in the primary disease. In all these the chest had been clear to physical examination on initial discharge from the hospital. However, in 7 instances the final roentgen film did not show complete resolution. This suggests a more conservative management of patients in whom the disease may seem to have cleared clinically but not roentgenographically.

COMPLICATIONS

Lungs.—Thirty patients (4 per cent) exhibited roentgen evidence of pleurisy, usually as cloudiness of the costophrenic angle. In only 15 was there clinical evidence of fluid. Thoracentesis was performed on 4, and the fluid was uniformly clear and sterile except that of 1 patient with empyema. In this patient, in whom the onset was characteristically that of atypical pneumonia, fever began subsiding on nonspecific therapy shortly after admission. A sudden rise in temperature was associated with a reddened throat, from which the beta hemolytic streptococus was isolated. Evidence of effusion became apparent, and culture of the fluid revealed the same organism. Purulent empyema developed with leukocytosis. Several months later this patient was still critically ill.

Hospitalization of patients with effusion was uniformly prolonged. An average of nineteen days was recorded for those whose condition was uncomplicated; in 1 instance, however, the patient was in the hospital for six months. Six cases of pleural effusion with 1 death [48] and 4 cases of empyema with 2 deaths [49] are described in the literature. One case of pulmonary abscess was described by Bowen.[6] There have been no cases of secondary staphylococcic pneumonia at Scott Field, such as Finland, Strauss and Peterson [50] described in an epidemic of an influenza-like disease in December 1940 and January 1941.

Atelectasis developed in the middle and lower lobes of the right lung of 1 patient with atypical pneumonia of the entire right lung. The course was relatively severe, with fever over 100 F. persisting for twelve days. However, recovery was complete in twenty-seven days.

Alimentary Tract.—Irritation of the alimentary tract was evidenced by pronounced nausea and vomiting (4 cases), diarrhea (8) or both (4) with little relief from atropine and bismuth; the stools revealed no pathogenic organisms. Symptoms usually subsided within one or two days but in 1 instance lasted ten days. Many patients were nauseated, apparently from gagging during paroxysms of coughing; sedation was usually effective. Reimann and Havens,[27b] discussing 400 patients with pneumonia and associated respiratory diseases, mentioned marked gastrointestinal upsets in 4 and catarrhal jaundice in 3.

Skin.—Herpes about the lips and the face was noted in 6 cases (1 per cent). Healing was prompt in those receiving sodium iodide intravenously. Dermatitis following the administration of sulfonamide compounds occurred in 2 cases.

Genitourinary Tract.—Four patients with albuminuria and 2 with glycosuria have been mentioned. Pronounced burning and smarting on urination developed in 2 patients (aged 23 and 30) with no urinary changes or findings of organic changes in the urinary tract. No specific treatment was given, and the symptoms subsided completely in two and five days.

Nervous System.—Neurologic complications occurred in 1 patient, aged 22, whose history of cough dated back one week.

The day before admission he noticed soreness and weakness in both legs. On the second hospital day he was unable to use his lower extremities, and reflexes of the ankles, the knees and the cremaster and abdominal muscles were absent; the patient remained alert. The third day his arms became weak; on the

48. Reimann,[27a] Maxwell,[21d] Green and Eldridge,[16] Goodrich and Bradford.[12]

49. Cass,[23b] Maxwell,[21d] Adams.[31b]

50. Finland, M.; Strauss, E., and Peterson, O. L.: Staphylococcal Pneumonia Occurring During an Epidemic of Clinical Influenza, Tr. A. Am. Physicians **56**:139-146, 1941.

fifth day the upper lip felt numb, and by the sixth day the right side of the face was paralyzed, with weakness of the left side of the face and absence of taste noted. Generalized weakness of the body, predominantly of the left side, progressed. The seventh day the patient was inarticulate and drowsy; he threshed about his bed when uncontrolled by sedation. From this day on he slowly recovered. By the fourteenth day strength in the extremities was almost normal, but a month later facial palsy was still present. Laboratory tests all gave normal values except for spinal fluid protein: On the fourth day the finding was 142 mg. per hundred cubic centimeters; on the seventh, 326 mg.; on the twenty-third, 112 mg.; on the thirty-fifth the value given by the Pandy test was reported as normal. The pneumonia was mild with the temperature never exceeding 100 F., and recovery was uneventful. Attempts to implicate the viruses of lymphocytic choriomeningitis, influenza, lymphogranuloma venereum, and meningopneumonitis failed.

In most reports of large series of cases mention is made of neurologic complications. In 5 cases meningismus has been described,[51] with no deaths, and in 4 encephalitis,[52] with 1 death.

Other Tissues.—Otitis media complicated 3 cases of atypical pneumonia; erysipelas and purulent conjunctivitis, 1 each. In all instances there was a response to sulfonamide compounds, and apparently the complication did not hinder pneumonic resolution.

ATYPICAL PNEUMONIA AS A COMPLICATION

Atypical pneumonia developed postoperatively in 7 patients and during the puerperium of 2. Diagnostic differentiation from the more characteristic postoperative bacterial pneumonias was not difficult as a rule. The combination of atypical pneumonia and asthma, bronchiectasis or hay fever occurred in 5 patients, all of whom had marked respiratory distress. In 1 patient convalescing from scarlet fever atypical pneumonia developed without evidence of streptococcic complications. In 2 patients with measles pneumonia developed with pulmonic infiltrations more extensive than described by Kohn and Koiransky[53] as occurring in uncomplicated measles. One case of combined malaria and pneumonia occurred, such as has been described by Campbell.[20]

Atypical pneumonia may be a serious complication of heart disease, as 5 fatalities have been reported. In the Goodrich and Bradford[12] series of 52 patients, gallop rhythm developed in 6, with electrocardiographic changes in 3. Green and Eldridge[16] noted that one third of their series showed mild tachycardia during convalescence and 3 transient cardiac enlargement. In 3 patients with cardiac disease (congenital, rheumatic and chronic myocarditis respectively) in this series pneumonia developed, but in none did the heart become decompensated or show other evidence of progressive cardiac injury.

DIFFERENTIAL DIAGNOSIS

Most of the pneumonic patients were sent to the hospital with a diagnosis of nasopharyngitis or bronchitis, and distinguishing the pneumonia from these infections of the upper respiratory tract was the primary problem. With auscultatory findings in the chest the problem was usually not difficult. In the remainder, unusual malaise, persistent nonproductive cough or protracted illness without obvious cause warranted roentgenographic examination of the chest. Certain types of bronchitis were difficult to distinguish from atypical pneumonia.

Once the diagnosis of pneumonia was made, the relative bradycardia, the leukopenia and the type of thoracic findings distinguished the atypical form from the pneumonias caused by bacterial infection. Technical laboratory methods are required to rule out the known virus and rickettsial pneumonias which closely simulate (and may include) this atypical disease.

Tuberculosis was suggested by the hazy, mottled roentgen appearance, especially when the disease occurred in the upper lobes, and by the frequency of blood-streaked sputum. The clinical illness, the sputum negative for acid-fast organisms and the rapidly clearing roentgenograms tended to rule out tuberculosis. On the other hand, the findings in initial roentgen films were occasionally interpreted as pneumonia, but because of the stability of the lesions, tuberculosis was eventually diagnosed.

No coccidiosis was observed in this series, but from the description of Dickson and Gifford[54] it would be difficult to rule out clinically, especially if the characteristic erythematous nodules in the skin were absent. Kneeland and Smetana[22a] described a patient with an erythematous eruption of the skin, and Markham[18] mentioned a patient with erythema multiforme without discussing the differentiation from coccidiosis.

EPIDEMIOLOGY

Predisposing Factors.—A study of the predisposing factors has not revealed any significant clues other than those commonly attributed to

51. Hornibrook and Nelson.[25] Kneeland and Smetana.[22a] Markham.[18]

52. Reimann.[27a] Scadding.[21b] Green and Eldridge.[16]

53. Kohn, J. L., and Koiransky, H.: Successive Roentgenograms of the Chest of Children During Measles, Am. J. Dis. Child. **38**:258-270 (Aug.) 1929.

54. Dickson, E. C., and Gifford, M. A.: Coccidioides Infections (Coccidioidomycosis): II. The Primary Type of Infection, Arch. Int. Med. **62**:853-871 (Nov.) 1938.

the simple infections of the upper respiratory tract. Many have a history of onset of symptoms with climatic change, fatigue or loss of sleep; most were unable to explain the onset. If atypical pneumonia is caused by a psittacine virus, as is suspected by some, it is of interest that fowl contract ornithosis (psittacosis) much more readily if they occupy congested cages.[55] or if they receive insufficient thiamine in the diet.[56]

Twenty-seven patients had been recently hospitalized with simple infections of the respiratory tract, at intervals of one day to three weeks, with the greatest concentration at two weeks. In those with one or two day intervals the diagnosis was probably unsuspected during the first hospitalization. The same statement might apply to the patients with the extended intervals; some may have been exposed to pneumonia during the initial illness, and certainly in a few the development of atypical pneumonia was a coincidence.

Eleven patients with apparently mild infections of the respiratory tract suddenly had marked aching and malaise after typhoid vaccinations, and were found to have pneumonia. Compared with the total number of soldiers receiving the vaccinations, this was a negligible incidence.

Incubation Period.—In an army camp, where there are multiple contacts, it is difficult to ascertain the one through which disease may have been transmitted. Study of the spread of pneumonia through the barracks revealed little as to the incubation period; for example, one barrack had 1 case one week, 2 the next, then none for four weeks. Few barracks had no recognized cases, yet no one barrack had over 8 throughout the year. The literature is almost unanimous with respect to an incubation of one to three weeks, most likely about two. Hufford and Applebaum [30] discussed a case with an apparent incubation of four days, and intimations of even shorter periods have been made.

Of 124 patients whose length of station at Scott Field was sought, 60 contracted pneumonia within four weeks, 43 in five to eight weeks, 15 in nine to twelve weeks and 4 in thirteen to sixteen weeks; the greatest concentration occurred at the end of the first week. As at all army posts, there is a constantly changing population at Scott Field. Gallagher [11] has suggested this as a factor; he noticed that the occurrences in his school community were highest among newcomers.

Contagiousness.—The small number of soldiers who contracted atypical pneumonia as compared with the characteristic rapid overwhelming spread of influenza or even of measles and scarlet fever among those susceptible suggests low contagiousness. There was no indication during 1942 of significant increase or decrease in the contagiosity or severity of atypical pneumonia.

In the medical group, 8 enlisted men, 4 nurses, 3 doctors and 2 dentists contracted the disease, an incidence considerably less than for the whole field, unlike the high incidence reported by Dingle and associates.[14b] Eaton, Beck and Pearson [35a] and Moss [29] have described severe forms which were unusually contagious. The suggestion of Smiley, Showacre, Lee and Ferris [8] and of Moore, Tannenbaum and Smaha [14a] that such measures as ward isolation and wearing of masks be carried out would be applicable in such cases but seems to have little place in military camps, where the disease is generally mild, where there has been widespread exposure before diagnosis is established and where apparently the rate of contagion is low.

One veterinarian was hospitalized with atypical pneumonia; he revealed that a number of animals, notably dogs, were being treated by the Veterinary Corps for a type of pneumonia which in many respects simulated that of human patients. No studies were made to see if there was any etiologic connection.

Seasonal Variations.—During 1942 there were two peaks of cases of simple infection of the respiratory tract (rhinitis, pharyngitis, tonsillitis, laryngitis, tracheitis, bronchitis): one in mid-February and one early in December; the low point occurred late in August. On the other hand, the cases of pneumonia averaged about 4 per 10,000 of population per week until June, then climbed rapidly during July to 10 to 15 per 10,000 per week. A secondary rise and the greatest single monthly concentration occurred during October (fig. 5). During the early months of 1943 a steady decline to early 1942 levels has become apparent. In the series of Dingle and his co-workers [14b] also the peak occurred during the summer. However, the majority of reports suggest that the seasonal peak occurs in the fall and early part of winter. Markham [18] feels that most cases are seen in the winter and spring.

In addition to the variations of incidence there were distinct clinical variations with change of

55. Meyer, K. F.; Eddie, B., and Yanamura, H. Y.: Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, Proc. Soc. Exper. Biol. & Med. **49**:609-615 (April) 1942.

56. Pinkerton, H., and Swank, R. L.: Recovery of Virus Morphologically Identical with Psittacosis from Thiamin-Deficient Pigeons, Proc. Soc. Exper. Biol. & Med. **45**:704-706 (Nov.) 1940.

season. Prehospital days of illness were fewer during the summer than during the winter. Onset during the summer was not only shorter but more abrupt and was characterized initially by malaise rather than by coughing. The duration of the acute stage of illness in the hospital showed three phases: During June and July it was four to six days; from August to October it was two days on an average, and during the early winter it increased again to three to five days. Hospitalization averaged twenty days during the summer and twenty-nine days during the winter. Leukocyte counts were distinctly lower during the summer (9,200) than during the winter (10,250). Thus, the summer pneumonia was milder, with more sudden onset, a brief acute stage and rapid convalescence.

Mode of Spread Through Camp (fig. 6).—The field is divided into segregated "areas" within which the soldiers are assigned to training schools. In one area, where the schools border a semicircle, the July wave of pneumonia struck each school in definite progression, with one to two weeks between their peaks. In another area the schools border a rectangle, and again the sequential progression was evident. Spread through the latter area was more rapid than through the former, and a contributing factor may have been the greater congestion.

ETIOLOGY

Etiologic studies have been directed primarily at the exudates from the respiratory tract. Pneumococci were uncommonly present and were chiefly of the higher types. Streptococcus viridans was consistently isolated, but no great significance is usually attached to it. Rhoads,[32] however, on the basis of studies of mice feels it may be important.

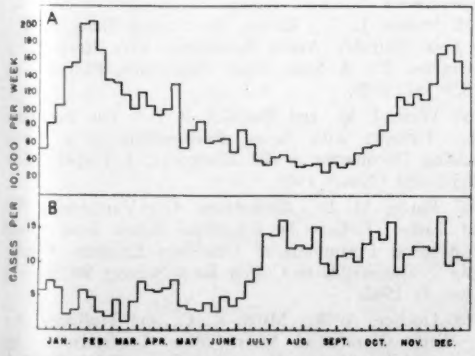

Fig. 5.—The incidence of atypical pneumonia (lower curve) compared with that of infections of the upper respiratory tract (upper curve) in 1942.

In most reported cases studies for viruses have failed completely to show any, but the exceptions are outstanding.[57]

Psittacosis Virus.—Eaton, Beck and Pearson [58a] isolated the virus of psittacosis from 4 cases of severe atypical pneumonia (2 fatal) and successfully transmitted it to mice, hamsters and guinea pigs. This virus was found to be closely related to the virus of meningopneumonitis isolated by Francis and Magill [58] from influenza-like cases in the 1934 and 1936 epidemics. In 4 Negroes with atypical pneumonia Dingle's group [14b] found unchanging high levels of complement-fixing antibodies for the virus of meningopneumonitis. Stickney and Heilman [59] identified the agent from one rather seriously ill patient as the psittacine virus. Meyer, Eddie and Yanamura,[55] Favour [23e] and Reimann, Havens and Price [60] found this virus responsible for sev-

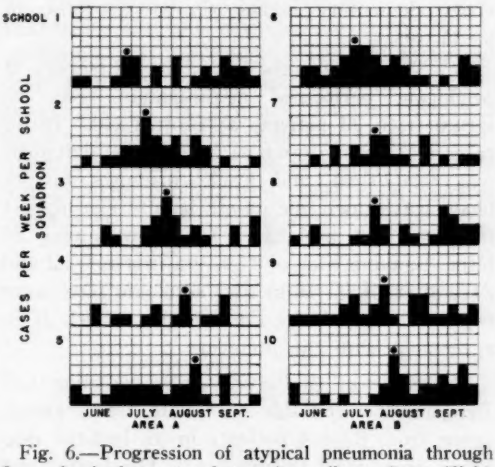

Fig. 6.—Progression of atypical pneumonia through five schools in each of two "areas" on Scott Field. Dots accentuate the progressing peaks in the schools.

57. Virus pneumonias, including atypical pneumonia, are completely summarized by Finland, M., and Dingle, J. H.: Virus Pneumonias; I. Pneumonias Associated with Known Nonbacterial Agents: Influenza, Psittacosis and Q Fever, New England J. Med. **227**:342-350 (Aug. 27) 1942. Dingle, J. H., and Finland, M.: Virus Pneumonias: II. Primary Atypical Pneumonias of Unknown Etiology, ibid. **227**:378-385 (Sept. 3) 1942.

58. Francis, T., Jr., and Magill, T. P.: An Unidentified Virus Producing Acute Meningitis and Pneumonitis in Experimental Animals, J. Exper. Med. **68**:147-160 (Aug.) 1938.

59. Stickney, J. M., and Heilman, F. R.: The Isolation of a Virus in Atypical Pneumonia, Proc. Staff Meet., Mayo Clin. **17**:369-375 (June 17) 1942.

60. Reimann, H. A.; Havens, W. P., and Price, A. H.: Etiology of Atypical ("Virus") Pneumonias, with a Brief Résumé of Recent Experiences, Arch. Int. Med. **70**:513-522 (Oct.) 1942.

eral cases of atypical pneumonia, as determined by complement-fixation tests. Favour [23e] has clearly shown the clinical relationship of atypical pneumonia and ornithosis (psittacosis). Baker [61] recognized an atypical pneumonia in cats which was apparently contagious for man and vice versa. The agent was transmissible from cats to mice and chick embryos, in which were recognized elementary bodies similar to those of psittacosis.

Dr. Thomas Francis Jr., at the University of Michigan, performed agglutination tests on serum from 23 patients at Scott Field. In all cases blood was drawn as soon as the diagnosis was established, and in 12 instances further blood was drawn one month later. The highest titer was 1:8, in 1 case. Of the remaining 34 tests, 4 gave a titer of 1:4, 9 a titer of 1:2 and 21 a titer of 0. Influenzal serologic tests were reported negative by Dr. Francis, which is in agreement with the literature.

Rickettsia of Q Fever.—Dyer, Topping and Bengston [62] were able to isolate this etiologic agent from 3 of 4 patients in an isolated outbreak of atypical pneumonia.[25] Hesdorffer and Duffalo [63] mentioned 1 case of mild pneumonia in which infection with Rickettsia diaporica was indicated by serum agglutination titers of 1:80 and 1:160. However, Green and Eldridge [16] reported no evidence of infection with this rickettsia in 15 patients.

Virus of Lymphogranuloma Venereum.—The Frei test was found to be positive in 5 of 8 patients by Rake, Eaton and Shaffer.[64] My associates and I have performed the test on 23 patients, using chick embryo antigen (Lygranum), with negative results. Dingle and associates [14b] found negative reactions in 7 patients. Eaton, Martin and Beck [35b] have demonstrated the antigenic relationship of the viruses of lymphogranuloma venereum and meningopneumonitis.

Viruses Not Previously Recognized.—Reimann,[27a] Reimann and Havens [27b] and Stokes, Kenney and Shaw [65] were able to produce pneumonia in ferrets by inoculating these animals with washings from the noses and throats of patients with atypical pneumonia. The viruses became attenuated or were lost in passage.

Weir and Horsfall [66] were able to produce pneumonia in wild mongooses with washings from the throats of 4 patients (types of illness not described). The causative virus was filtered through Berkefeld V and N candles, was not inactivated by glycerin, by freezing or by drying in vacuo, and was propagated on the chorioallantoic membranes of chick embryos.

Eaton, Meikeljohn, Vantterick and Talbot [67] transmitted a virus to cotton rats with sputums from 17 of 18 patients who had atypical pneumonia. This virus was filtered through Berkefeld N candles in 2 of 6 instances. It was not transmissible to common laboratory animals.

Adams, Green, Evans and Beach [31c] studied a severe form of pneumonia in young infants. No virus was found, but intracytoplasmic inclusion bodies were detected in pulmonary epithelial cells and in cells in smears of material obtained from throats.

Viruses are apparently inherent in certain animals (mice [68] and hamsters [69]), and serial passages may increase their virulence to the point of producing pneumonia. This should be taken into consideration in etiologic studies of atypical pneumonia.

61. Baker, J. A.: A Virus Obtained from a Pneumonia of Cats and Its Possible Relation to the Cause of Atypical Pneumonia in Man, Science **96**:475-476 (Nov. 20) 1942.

62. Dyer, R. E.; Topping, N. H., and Bengston, I. A.: An Institutional Outbreak of Pneumonitis: II. Isolation and Identification of Causative Agent, Pub. Health Rep. **55**:1945-1954 (Oct. 25) 1940.

63. Hesdorffer, M. B., and Duffalo, J. A.: American Q Fever, J. A. M. A. **116**:1901-1902 (April 26) 1941.

64. Rake, G.; Eaton, M. D., and Shaffer, M. F.: Similarities and Possible Relationships Among Viruses of Psittacosis, Meningopneumonitis, and Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **48**: 528-531 (Nov.) 1941.

65. Stokes, J., Jr.; Kenney, A. S., and Shaw, D. R.: A New Filtrable Agent Associated with Respiratory Infections, Tr. & Stud., Coll. Physicians, Philadelphia **6**:329-333, 1939.

66. Weir, J. M., and Horsfall, F. L.: The Recovery from Patients with Acute Pneumonitis of a Virus Causing Pneumonia in the Mongoose, J. Exper. Med. **72**:595-610 (Nov.) 1940.

67. Eaton, M. D.; Meikeljohn, G.; Vantterick, W., and Talbot, J. C.: An Infectious Agent from Cases of Atypical Pneumonia of Unknown Etiology Apparently Transmissible to Cotton Rats, Science **96**:518-519 (Dec. 4) 1942.

68. Dochez, A. R.; Mills, K. C., and Mulliken, B.: A Virus Disease of Swiss Mice Transmissible by Intranasal Inoculation, Proc. Soc. Exper. Biol. & Med. **36**:683-686 (June) 1937. Gordon, F. B.; Freeman, G., and Clampit, J. M.: A Pneumonia-Producing Filtrable Agent from Stock Mice, ibid. **39**:450-453 (Dec.) 1938. Horsfall, F. L., and Hahn, R. G.: A Pneumonia Virus of Swiss Mice, ibid. **40**:684-686 (April) 1939. Nigg, C.: An Unidentified Virus Which Produces Pneumonia and Systemic Infection in Mice, Science **95**:49-50 (Jan. 9) 1942.

69. Pearson, H. E., and Eaton, M. D.: A Virus Pneumonia of Syrian Hamsters, Proc. Soc. Exper. Biol. & Med. **45**:677-679 (Nov.) 1940.

SUMMARY

Seven hundred and thirty-eight cases of atypical pneumonia were recognized during 1942 at the Station Hospital, Scott Field, Ill. Serious complications were rare; there were no fatalities. The disease showed epidemic tendencies during the late summer and fall when common diseases of the respiratory tract were at a minimum. Seasonal clinical variations were apparent.

Atypical pneumonia attacks congregated groups of people, especially young adults. The degree of contagion and the recoverability of the etiologic agent seem to vary with the severity of the illness. After an incubation period of one to three weeks, there develops in the exposed person a nonproductive cough, accompanied or followed by fever, aching, weakness and loss of appetite. Cough is the most troublesome symptom but tends to be relieved within a few days as the fever diminishes by lysis. The pulse rate, the respiratory rate and the leukocyte count are little elevated in uncomplicated cases, and there is a lack of such clearcut findings as are observed with pneumococcic pneumonia. Prolonged convalescence is the rule, and if a patient is seen for the first time during convalescence, neurocirculatory asthenia may be suggested. Complications are uncommon, but the occasional development of effusion and empyema warrants recognition of the primary disease. From a military standpoint the time lost is significant. Over 20,000 man-days (or 55 man-years) were lost at Scott Field during 1942 from atypical pneumonia.

HODGKIN'S DISEASE—INCIDENCE AND PROGNOSIS

A STATISTICAL CORRELATION WITH THE CLINICOPATHOLOGIC PICTURE

S. R. BERSACK, M.D.
WASHINGTON, D. C.

At the conclusion of his article on Hodgkin's disease in the 1939 University of Wisconsin Symposium on Blood, Krumbhaar [1] succinctly commented: "Thus we see that in general, the problems of Hodgkin's disease in the past generation remain the problems of today. We still do not know whether it is an infectious granuloma or a neoplasm, and, therefore, we are ignorant of its pathogenesis; we have no specific laboratory diagnostic test other than the biopsy examination. We have no means of predicting how long a given case will survive; and we have no specific form of treatment."

It was with the hope of throwing some light on the two last-named factors that this study was undertaken. The review also included a careful search for clues as to a common predisposing factor or etiologic agent. However, the main question posed was: Are there any criteria for predicting the course and duration of the disease?

A cursory review of any series of cases of Hodgkin's disease immediately suggests the desirability of a biopsy study. When the first few cases were analyzed it became apparent that a restudy of the biopsy slides is not just a desideratum but a necessity. The variations in the manifestations and severity of the disease must, a priori, be at least partially reflected in the pathologic picture. Soon 2 biopsy descriptions were encountered reading "cellular Hodgkin's disease"; 1 patient was dead, having had a total duration of twelve months, and the other was alive, with a total duration of two hundred and thirty-six months. It then became clear that a restudy of all the biopsy and autopsy material with attention to the minute details is a sine qua non.

1. Hodgkin's lymphoreticuloma { Typical / Atypical
2. Hodgkin's granuloma
3. Hodgkin's lymphoma { Typical / Atypical

MATERIAL

The clinical histories of 244 cases were analyzed. These represent the cases of all the patients with Hodgkin's disease who were admitted to the Edward Hines Hospital during the eleven years from 1930 to 1940, inclusive. Eight patients had no biopsies. The 5 dead patients had an average total duration of the disease of 51 months. Of the 3 patients still alive, 1 had it for 156 months, another for 132 months and the third for 36 months. One can thus readily see what havoc in the statistics of a small series of cases can be produced by the inclusion of cases without biopsy confirmation.

At the conclusion of the study it was found necessary to eliminate 11 more cases, 4 because of incomplete data and the other 7 because the diagnosis of Hodgkin's disease had been made erroneously. Enumeration of the corrected diagnoses is instructive, in that it shows with what entities Hodgkin's disease may be confused. The following are the corrected diagnoses: reticulum cell sarcoma, 2 cases, and chronic lymphadenitis, fungous infection, lymphoepithelioma, lymphosarcoma and benign lymphoma, 1 case each. (The condition in the last case defies more specific classification than as benign lymphoma.)

Two hundred and twenty-five cases of verified Hodgkin's disease were thus left in which microscopic studies had been made. On the basis of a restudy of the slides from 186 cases, inclusive of 67 autopsies, the following clinicopathologic classification was arrived at.

1. Generalized
2. Superficial multiple glandular
3 Localized

NOMENCLATURE

A. Histologic Definitions.

1. Hodgkin's Lymphoreticuloma: This type has a prevalence of reticulum cells or frequent mitoses or both. Large or medium-sized lymphocytes when associated with frequent mitoses have a significance analogous to the reticulum cells; hence the inclusion of "lympho" in the term lymphoreticuloma.

2. Hodgkin's Granuloma: This type, which occurred in the majority of the cases, shows the typical features of pleomorphism, Sternberg-Reed cells and a moderate degree of fibrosis.

3. Hodgkin's Lymphoma: This type shows destruction of glandular architecture and only a slight tendency to pleomorphism, with a moderate persistence or prevalence of the lympho-

From the Tumor Service, Veterans Administration Facility, Hines, Ill.

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1. Krumbhaar, E. B.: The Present Status of Hodgkin's Disease, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, pp. 148-166.

cytic element. Most of the lymphocytes are of the small variety. Some medium-sized lymphocytes may be present, but without any associated frequent mitoses. It is with this type that occasionally one may have to make the diagnosis of Hodgkin's disease in the absence of Reed or Sternberg cells. One must be sure, however, to segregate cases in which the diagnosis is so made in any statistical study with classification into typical and atypical forms. The word typical would refer mainly to the important element of Sternberg-Reed cells.

B. Clinical Stages.—From a clinical standpoint one recognizes three stages or degrees of involvement: the localized, the superficial multiple glandular and the generalized. The pathologic and clinical observations were therefore analyzed separately for these three stages or phases of involvement.

ANALYSIS

A. *Reference Point for Evaluation of Duration.*—Several authors had already previously pointed out, and more recently Slaughter and Craver again emphasized the point, that one does not obtain a true picture of Hodgkin's disease by taking a single reference period for evaluation of duration of the disease. There is an inherent fallacy in counting duration from the time of biopsy or of beginning of treatment. This fallacy lies in the great variation in the period elapsed between the onset of the disease and the time the patient presents himself to the physician or institution where a biopsy is made or a definitive form of treatment is resorted to. In favor of this reference point is the fact that the time of biopsy or of beginning of treatment is definitely known and is a matter of record. This reliability is contrastedly lacking in the data as to onset obtained from the patient. They are especially vague in cases in which the first manifestations are not glandular enlargement but systemic complaints, such as weakness, loss of weight, fever and osseous pain. The duration after the patient's admission to the hospital, taken by itself, has little significance. Some patients have had previous hospitalizations at other institutions and in fact may have had several courses of irradiation.

In view of the aforementioned considerations, it was decided to represent each case by four numerical values in the form of two fractions, thus —

$$\frac{\text{Postnodal Duration}}{\text{Postbiopsy Duration}}; \quad \frac{\text{Existence of Nodes Prior to Definitive Treatment}}{\text{Total Duration After Onset of Symptoms}}$$

The first numerator stands for the total duration in months after the onset of glandular enlargement. The first denominator denotes the number of months elapsed between the biopsy or the beginning of treatment and death or the last follow-up of those patients who are still alive. The second numerator expresses the number of months that known glandular enlargements have existed prior to institution of definitive therapy. The second denominator is used to denote the total duration of symptoms in those cases in which the first manifestation was cutaneous involvement or a systemic complaint.

B. *Correlation of Duration with Histologic Picture.*—1. Generalized Lesions: When the histologic picture is viewed as a whole one can readily divide the cases into instances of typical Hodgkin's disease and cases in which the condition for one reason or another is atypical. In the latter, sections may fail to exhibit the important typical element, the Reed cell, and they usually present a prevalence of cells of the lymphocytic or reticuloendothelial series. When this gross pathologic yardstick was applied, 96 (42.7 per cent) patients with typical generalized disease were found. These had an average duration of 29.2/19.2; 16.8/31.3. Six of the 96 patients are still alive. One has a total duration of 75 months and another of 50 months. The remaining 4 thus far have an average duration of only 24 months.

Of the 29 patients with an atypical generalized form of Hodgkin's disease, 12 formed a distinct group. Their lesions were characterized by prevalence of reticulum cells and/or frequent mitoses. These were not reticulum cell sarcomas but atypical Hodgkin's lymphoreticulomas. In table 1 the clinical course of this subgroup is graphically compared with that of the remainder of the group with an atypical generalized form (Hodgkin's lymphoma). This segregated subgroup (with atypical Hodgkin's lymphoreticuloma) had a duration of 8.6/4.2; 5.2/9.6, as contrasted to a duration of 61.0/49.7; 29.0/64.7 for the remainder of the patients with atypical disease (atypical Hodgkin's lymphoma).

A similar subgroup with lesions exhibiting prevalence of reticulum cells and/or frequent mitoses (typical Hodgkin's lymphoreticuloma) was segregated from the 96 patients with a typical generalized form. Seventeen such patients had an 18.7 month total duration, as against 34.9 months for the remainder of the group, and a duration of 10 months after the beginning of treatment, contrasted to 21.1 months for the remainder of the group. It is to be noted that the total duration for the patients with typical generalized Hodgkin's disease with prevalence of reticulum cells and/or mitoses is about twice as much as the period for the groups with a

similar atypical form (18.7 as against 9.6 months). Evidently it takes time for some pleomorphism and Reed cells to develop. The lesions which are more malignant never have a chance to acquire these characteristic features to any degree of prominence.

2. Superficial Lesions: The same major pathologic criterion of typicality applied to the 55

TABLE 1.—*Average Life Expectancy of Patients with Hodgkin's Disease After a Biopsy Which Reveals Typical Sternberg-Reed Cells*

	Mitosis	Prevalence of Reticulum Cells	Fibrosis	Number of Cases	Average Duration in Months After Biopsy	
Generalized	+	..	..	21	8.7	
	..	..	+	..	17.3	
	—	—	..	..	22.2	
	—	— and also minus prevalence of medium lymphs	+	..	28.1	
	Total			66	12.4	
Superficial	+	..	..	9	11.0	
	..	..	—	11	12.6	
	—	—	..	12	28.5	
	..	..	+	10	30.2	
	—	..	+	8	35.6	
	—	..	+ and intact capsule	2	41.0; 78.0 →	
	Total			25	21.0	
Localized	+	+	..	9	27.6	
	—	—	..	..	53.7	60 → Three alive 32 → 103 →
	Total			22	39.0	Seven alive
	Thirteen cervical				43.4	
	Three axillary				54.6	
	Two retroperitoneal				35.5	
	Four inguinal				15.0	

cases with only superficial multiple glandular involvement yielded 31 with a typical histologic picture. Twenty-six of these had an average duration of 48.1/36.0; 28.2/50.0. Three of the patients are alive, 1 with a duration of 68 months, 2 with duration of 33 months each.

In 5 cases with typical changes there were the additional features of prevalence of reticuloendothelial cells and/or mitoses. In these the disease had a much shorter course, averaging 10 months after biopsy and a total of 21 months after the appearance of nodes. In the cases of the analogous atypical form (4) the duration was 8 and 12.2 months respectively. This, again, is consistent with the conclusion that frequent mitoses associated with prevalence of reticuloendothelial cells and lacking in Reed cells and pleomorphism spell a short course. A striking contrast was presented by the 11 remaining cases of atypical superficial Hodgkin's disease. These had an average of 67.6 and 86.4 months postbiopsy and postnodal duration, respectively. Five of the 11 patients are alive, with an average total duration of 159 months. One of the 5 has adenopathy and is in poor condition. The other 4 have small residual lymph nodes and are in good general condition.

3. Localized Lesions: The 28 patients who had localized cervical or axillary adenopathy exhibited a much more favorable course. The average duration was 96.6/53.1; 46.7/97.3. In table 6 the cases of localized cervical Hodgkin granuloma are graphically contrasted to those of localized inguinal Hodgkin granuloma. A rather surprising observation was the fact that the typical localized inguinal Hodgkin granuloma showed the least favorable course among the localized group of lesions. One is tempted to suggest that inguinal involvement signifies wide dissemination.

C. Correlation of Duration with Individual Cellular and Stromal Components of the Biopsy Sections.—1. Sternberg-Reed Cells: Given a biopsy specimen with typical Sternberg-Reed cells, what is the patient's life expectancy? The important factors of mitosis, fibrosis and prevalence of reticulum cells were evaluated independently and in combinations. The duration after biopsy is listed in table 1.

The hyperchromatic Sternberg cells failed to show any differential prognostic value when compared with the vesicular Reed cells. Similarly, the giant cells of the Sternberg-Reed type, which were encountered in approximately half of the cases, and the finding of Reed cells lying in empty spaces did not show any added significance other than that of the usual Sternberg-Reed variety.

2. Reticuloendothelial Cells: Statistical evaluation of prevalence or predominance of reticuloendothelial cells as a single factor was impossible, since almost all these patients had mitoses. Table 2 enumerates the duration for each of the three clinical phases of involvement. Only 1 example each of localized, superficial and generalized

TABLE 2.—*Duration of Hodgkin's Disease Exhibiting Prevalence of Vesicular Variety of Reticulum Cells*

	Number of Cases	Average Duration After Appearance of Nodes	Average Duration After Biopsy
Generalized	11	14.2	5.6
Superficial	5	41.2	12.2
Local	2	51.0	35.0
		23.0	4.0

lesions without mitosis were found with the vesicular reticulum cell variety. Also 2 patients had superficial lesions without mitosis of the punctate reticuloendothelial variety. These 2 patients lived only three months after biopsy. The observations in these few cases—though not statistically significant—seem to indicate that the prevalence or predominance of reticuloendothelial cells by itself produces a short course for the

patients with superficial and generalized lesions. With localized lesions one must be on guard against mistaking a reticulum cell sarcoma for a reticulum cell variety of Hodgkin's disease.

3. Lymphocytes: Prevalence of medium-sized to large lymphocytes, especially when they are associated with cells resembling the punctate variety of reticuloendothelial cells, has the same prognostic value as the presence of the latter. Contrasted to this is the much better prognosis of the 14 cases in which there was predominance of medium-sized lymphocytes without the association of reticuloendothelial cells. Most of this group were instances of atypical or only somewhat typical lesions. The duration in the 5 cases of generalized lesions averaged 43.0/37.5; 14.2/58.2; 1 patient is still alive. The duration in the 3 cases of superficial lesions averaged 71.0/63.6; 19.3/71.0; 2 patients are alive. The 6 cases of localized lesions had an average duration of 103.0/76.5; 44.0/103.0; 4 patients are alive.

A still longer course was found in the group of 5 of 7 cases in which there was a predominance of small lymphocytes without the association of either reticuloendothelial cells or mitoses. These averaged 69.0/56.7; 27.3/69.0.

4. Polymorphonuclears: Of 18 cases with a prominent polymorphonuclear component, 3 had an extremely short course, 4.6 months after biopsy. In these 3 cases polymorphonuclear cells were prevalent throughout the lymph nodes and apparently there was the added element of frank infection. In 6 other cases of typical generalized lesions with polymorphonuclear cells the postbiopsy duration averaged 30.5 months. This is a much longer course than the expected 12.4 months, as shown in table 1. A shift to the right in the polymorphonuclear cells was associated in most cases with a slightly more favorable course. No correlation of frequency of polymorphonuclear cells with clinical manifestations of fever could be established.

5. Plasma Cells, Eosinophils: No correlation of the number of these cells with longevity was evident. Prevalence of plasma cells is found more often in cases of localized involvement, especially in inguinal adenopathy and in glands involved for a short time, i. e., early development.

6. Fibroblast-like Cells or Derivatives Thereof: Fibroblast-like derivatives may signify a reaction of the body to a weak dose of the noxus and thus be associated with a fairly long course. The finding of such fibroblastic derivatives at biopsy, however, does not necessarily signify a long postbiopsy course. The involvement of lymph nodes and the disease may have existed a long time before any local or systemic complaints brought the patient to the hospital.

Preservation of Follicles: No special effect on duration could be attributed to preservation of a few peripheral follicles, except in those cases in which it constituted one of the elements of atypicality.

Vascularity: Similarly, vascularity of the lymph nodes is another and important element in the atypical picture. Eleven cases of such vascularity were found in this series. Three patients with typical lesions and 1 with atypical lesions with mitosis had a course consistent with their histologic pictures. Of the remaining 7 patients, 6 are alive, with durations averaging 128.3 months postnodal and 74.3 months postbiopsy. The seventh patient died 38 months after biopsy. Five of these 7 patients had localized cervical lesions, 1 localized inguinal and 1 generalized.

D. Correlation of Duration with Clinical Manifestations.—1. Cutaneous Manifestations: Forty-three patients had complaints referable to the skin. Thirty had pruritus; in 21 of these this was the only cutaneous manifestation. The patients with typical generalized lesions had durations consistent with the histologic picture. Five patients with atypical generalized involvement had an average duration of 82.0/50.4; 31.0/82.0. The symptoms of 2 patients with an atypical histologic picture began with involvement of the skin. The first patient is still alive (60/60; - / 262→). The second, a man of 62 years, died (9/8; - / 29).

There appears to be a disproportionate number of patients with atypical forms of the disease among those with cutaneous manifestations. Twenty-six of the 43 patients had atypical lesions—an incidence of 60.2 per cent, as against 25.8 per cent incidence of atypical lesions in the whole series.

2. Osseous Involvement: The incidence of infiltration of bone is unavoidably dependent on the thoroughness of roentgen examinations and autopsies. It will therefore vary considerably in reports from various sources. Thirty-three cases with such infiltration were met in this series (14.7 per cent). Thirteen of the patients had typical generalized forms of Hodgkin's disease and had an average postnodal duration of 41.6 months; 3 patients with typical superficial lesions had an average duration of 87.6 months. The duration in these cases is considerably above that in the general series. Apparently osseous involvement occurs and/or is detected in cases lasting longer.

A cursory scanning through the duration of the cases with osseous involvement tempts one

to postulate some protective influence of osseous infiltration. Actually, no basis for such a conclusion can be established. The patients whose biopsies showed prevalence of reticulum cells and/or mitoses had the usual short course. Ten patients with typical generalized lesions had an average duration of 17 months, and that of 3 with typical superficial lesions was 6.6 months, after detection of osseous infiltration.

3. Fever: Considered independently, exhibition of fever had no perceptible influence on the course of Hodgkin's disease.

E. Incidence of Hodgkin's Disease.—Most textbooks of medicine and pathology state that Hodgkin's disease is mostly a disease of early middle age, 20 to 40 years. Uhlenhuth [2] has contradicted this teaching. He has claimed that an analysis of the number of people dying each year from Hodgkin's disease relative to the number of people of that age group in the population shows a steady increase in incidence with age. Thus he has computed that at 10 years there is an incidence of 62 per 10,000,000, and at 30 years, of 180 and that at 60 years the incidence has increased to 220, with a slight decrease after 60 years. The reason why it is thought to be most prevalent in the 20 to 40 year age group is that absolutely this age group is the most numerous among adults.

TABLE 3.—*Incidence of Hodgkin's Disease by Decades in the Cases of Typical Generalized Lesions*

	20-29	30-39	40-49	50-59	60-69
First 48 cases.....	1	33	12	1	1
Last 48 cases.....	1	6	35	3	3

This series of 225 cases tends to support Uhlenhuth's contention. The material, which covers eleven years, represents the cases of Hodgkin's disease from a fairly constant fraction of a definitely segregated age group. In 1930 the average age of the World War I veteran was about 36 years. During the first five years of this selective study period (1930 to 1935) the majority of the veterans were in the late thirties. In the last five years the majority of the veterans were in the forties. This is consistent with the finding of an average age of 37.4 years at onset of the disease in the first 39 cases of generalized typical Hodgkin's disease exclusive of those showing prevalence of reticulum cells and mitoses. During the last five years, as the veteran population grew older, the last 39 such cases showed an average age of 43.5 years at onset. This makes a difference of (43.5 minus 37.4) six and one-tenth years, corresponding closely with the elapsed five and a half years in the aging of the veterans. Table 3 lists the incidence by decades. It clearly shows that Hodgkin's disease is not a disease mostly of the 20 to 40 year age period. This fact is further strikingly brought home by the occurrence of approximately the same number of cases (20) per year in the eleven year period, even though one started with a fairly constant segment of population of veterans averaging 36 years old and concluded with veterans of 47 year average age.

TABLE 4.—*Duration by Decades of Generalized Typical Hodgkin's Disease Exclusive of Hodgkin's Lymphoreticuloma*

Decade	Number of Cases	Number of Patients Still Alive	Postnodal Duration
30-39.....	34	1	42.2
40-49.....	37	4	23.6
50-59.....	4	None	20.5

Gilbert concluded that the most favorable cases are those in which the patients are in the twenties and thirties. When the typical cases of generalized lesions were segregated into decades, a gradually shorter course was found to be associated with increasing age, as detailed in table 4.

The 4 patients with Hodgkin's disease who were in the sixties exhibited a still much shorter postnodal course, namely 12 months. One could readily attribute this short course to the fact that the average life expectancy has its termination at or in this decade. However, closer scrutiny brought out the fact that the lesions of 3 of the 4 patients in the sixties had the histologic feature of prevalence of reticulum cells and/or mitoses. A similar tendency for prevalence of reticulum cells and/or mitoses to occur in the older age group was found throughout the whole series. Details are given in table 5.

TABLE 5.—*Relation Between Age of Onset of Hodgkin's Disease and Prevalence of Reticulum Cells and/or Mitoses*

	Average Age at Onset of Hodgkin's Disease			
	Without Prevalence of Reticulum Cells and/or Mitoses		With Prevalence of Reticulum Cells and/or Mitoses	
Type of Disease	Number of Cases	Average Age at Onset, Yr.	Number of Cases	Average Age at Onset, Yr.
Typical generalized.....	79	40.4	17	46.4
Atypical generalized.....	17	39.3	12	46.6
Typical superficial.....	26	38.7	5	42.0
Atypical superficial.....	11	40.4	4	42.2

2. Uhlenhuth, P., and Wurm, K.: Present Status of Knowledge on Etiology of Hodgkin's Disease, Deutsche med. Wchnschr. **66**:785, 1940.

F. Weighting of Material.—This series of 225 cases of Hodgkin's disease consisted entirely of male patients, the majority of whom were in the lower income level. Hence the statistical figures should be weighted for sex and economic stratum. Wallhauser [3] mentioned hard work, poor food and intercurrent infection in relation to duration of the disease and quoted Gemmell,[4] in whose opinion estrogen has a protective value. Gilbert,[5] too, has expressed the opinion that the disease is milder in women. There were 12 women among the 16 survivors in his reported 73 cases of Hodgkin's disease. Slaughter and Craver,[6] however, did not find such a great difference in prognosis between males and females. In their series the males had a 16 per cent five year survival rate and the females 21 per cent. A definite opinion as to the comparative mildness of Hodgkin's disease in women is not possible without reference to and statistical analysis of the histologic picture.

SUMMARY

The clinical histories of 225 cases of Hodgkin's disease were reviewed and the microscopic slides of 186 of these cases, inclusive of 67 autopsies, were restudied.

Before one can be in a position to comment on the role various clinical factors play in the course of the disease one has to know the exact disease entity and histologic picture that one is dealing with.

In the great majority of cases there is sufficient uniformity in the several sections of one lymph node or in several simultaneously taken biopsy specimens from varying sites to warrant the characterization of each case on the basis of the histologic picture.

The outstanding ominous determinant of prevalence of reticulum cells with associated mitoses is statistically of such compelling nature as to warrant—nay, require—a nomenclature based primarily on the histologic features shown by biopsy. Such a nomenclature, listing the types in the order of increasing duration of the course, has been suggested.

The favorable elements in the atypical histologic picture of Hodgkin's disease comprise preservation of follicles, intact capsule, fibrosis, trabeculation or tendency to giant follicle formation, vascularity, presence of derivatives or fibroblast-like cells and persistence in abundant numbers of the small lymphocytic element of the node.

The extent of involvement bears a direct relation to the course, being second in importance only to the histologic features. Truly localized lesions in the cervical and axillary regions do occur, and these have a much more favorable prognosis.

The inguinal involvement, though clinically localized, appears to have the same significance as generalized spread.

The incidence of Hodgkin's disease is not confined mostly to the 20 to 40 year age group. This fact is strikingly brought home by the occurrence of the same number of cases (approximately 20) per year in the eleven year period, even though one started with a fairly constant segment of population of veterans of 36 years average age and concluded with veterans of 47 years average age.

This study showed increased frequency of the lymphoreticuloma type of Hodgkin's disease, with its sarcomatous features, in the older age group. This contributes to the worse prognosis of the disease in older patients. In fact, the reported incidence of Hodgkin's disease in the older age group will vary as one does or does not include the lymphoreticuloma type, especially in cases in which autopsy is not performed, so that the pathologist is not given the opportunity to see the typical picture of Hodgkin's disease developed.

The average duration in the groups of cases of sufficient number for statistical significance is summarized in table 6. The patients have been segregated according to the histologic picture shown by biopsy and the extent of involvement.

TABLE 6.—*Average Duration in Months of Two Hundred and Twenty-Five Cases of Hodgkin's Disease*

Generalized	Total After Onset of Symptoms	After Appearance of Nodes	After Biopsy
Hodgkin's lymphoreticuloma, typical..	18.7	16.5	10.6
Hodgkin's lymphoreticuloma, atypical	9.6	8.6	4.2
Hodgkin's granuloma.....	34.9	32.3	21.8
Hodgkin's lymphoma, atypical.....	64.7	61.0	49.7
Superficial Multiple Glandular			
Hodgkin's lymphoreticuloma, typical..	21.0	21.0	10.0
Hodgkin's lymphoreticuloma, atypical	14.0	12.2	8.0
Hodgkin's granuloma.....	50.0	48.1	36.8
Hodgkin's lymphoma, atypical.....	107.7	86.4	67.6
Localized			
Hodgkin's granuloma, inguinal.....	43.8	43.8	19.6
Hodgkin's granuloma, cervical (the dead patients).....	84.6	84.6	47.6
Hodgkin's granuloma, cervical (patients still alive).....	133.6→	133.6→	128.0→

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GROUP A HEMOLYTIC STREPTOCOCCUS ANTIBODIES

III. A STUDY OF THE SIMULTANEOUS INFECTION OF A LARGE NUMBER OF MEN BY A SINGLE TYPE *

LOWELL A. RANTZ, M.D.
WITH THE TECHNICAL ASSISTANCE OF GEORGIANA DOLE
SAN FRANCISCO

It is well known that varying amounts of circulating antibacterial and antitoxic antibodies are present in the serums of many persons, that increases in these immune substances may be expected to occur following infections and that the magnitude of the immune response differs from individual to individual. Rarely, if ever, have actual measurements of these antibodies been made for large groups of human subjects simultaneously infected with a single strain of micro-organism.

An unusual opportunity to perform such studies became available recently when an outbreak of streptococcic pharyngitis occurred in an Army camp. Many of the clinical details of this epidemic have been described elsewhere,[1] but they may be summarized here. Within sixty hours more than 300 men were admitted to the hospital suffering from typical hemolytic streptococcus tonsillitis or pharyngitis of varying degrees of severity. Approximately 20 per cent of them had a rash and presented the clinical picture of scarlet fever. None of the men died, and only minimal suppurative or nonsuppurative complications were observed. All were treated with the usual amounts of sulfathiazole.

The source of the epidemic could not be traced, but hemolytic streptococci, all of which were mucoid members of group A and of the Griffith subtype 15, were demonstrated in nearly all of the throat cultures obtained from approximately 10 per cent of the group. Infection in similar epidemics usually has occurred through the consumption of milk contaminated by hemolytic streptococci, and it is reasonable to suppose that these men simultaneously ingested streptococci in some article of food.

For the purpose of this study, 118 men, who entered the hospital during one interval of twenty-four hours and who had thus undergone similar incubation periods before the appearance of active infection, were selected for observation. Serums were collected on the fourth day of the disease and again on the twenty-first day. Clinical observations were also made in each case, some of which will be presented in this report.

The antistreptolysin titers of all of the serums were determined, as were agglutinins for the homologous type of streptococci. These observations will now be described in detail.

METHOD

Serums were collected in the usual manner and stored at 5 C. until used. Antistreptolysin titers were determined by the method of Coburn and Pauli,[2] a single lot of streptolysin being used for all tests. Agglutinins were studied by a slide technic previously described.[3] The methods for the performance of throat cultures and for the serologic identification of the isolated hemolytic streptococci have also been presented elsewhere.[4]

RESULTS

Antistreptolysin Titers.—Initial Levels: The distribution of the studied subjects by initial antistreptolysin titers is presented in table 1 and the chart. It will be observed that the group with titers from 50 to 250 units included nearly

From the Department of Medicine, Stanford University School of Medicine, Stanford University Hospitals.

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all of the men and that no definite peak incidence occurred within this range; 39.8 per cent had levels above 125 units.

The relationship between the initial antistreptolysin titers and the nature of the patient and the clinical disease was studied, and two facts emerged: First, there was no definite correlation between the presence of a rash, indicating a lack of immunity to the erythrogenic toxin of the hemolytic streptococci, and the initial antistreptolysin titer. Subjects with rash were found to be evenly distributed through the entire antibody range. Second, as the antibody levels increased from 50 to 250 units, there was a fairly regular decrease in the percentage of tonsillectomized patients. These data are summarized in table 1.

Antistreptolysin Response.—The antistreptolysin titers of 118 patients were determined twenty-one days after the onset of the acute illness, and the results were compared with the initial titers, obtained on the fourth day. The results are

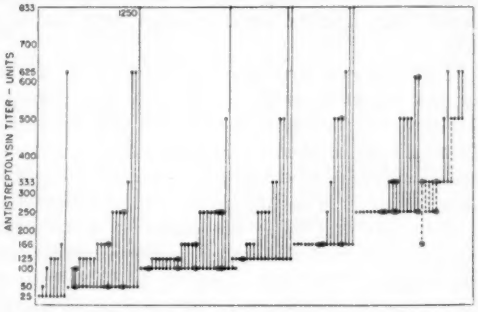
TABLE 1.—*Distribution of Subjects According to Initial Antistreptolysin Titer*

Initial Anti-streptolysin Titer	All Subjects	Per Cent of All Subjects	Number with Rash	Per Cent with Rash	Number Tonsillectomized	Per Cent Tonsillectomized
25	8	6.8	..	....	1	12.5
50	21	17.8	4	19.0	6	28.5
100	25	21.2	6	24.0	6	24.0
125	17	14.4	1	5.9	2	11.7
166	17	14.4	3	17.6	1	5.9
250	18	15.2	6	28.5	1	5.5
333	8	6.8	3	37.5	2	25.0
500	4	3.4	..	....	..	....
Total	118		23		19	

portrayed in the chart. The most striking feature of these observations is the great difference in magnitude of antistreptolysin response within the group. Thus, there was a fourfold or greater increase in titer in 11 per cent and no increase in 28 per cent. No correlation was observed between the presence or absence of rash or the severity of the clinical disease and the antistreptolysin response.

Certain relationships between these antibody levels in the acute and in the convalescent stage of the disease are further analyzed in table 2. The subjects have been divided into groups on the basis of the initial antistreptolysin titer, and it will be noted that the average final titer increased from lower to higher levels. Most interesting, however, was the fact that the ratio of average final titer to initial titer decreased. The patients with initial levels below 100 units had an approximately fivefold augmentation of titer, whereas those with levels of 250 or more units exhibited little increase. Similar results were observed when the actual number of men showing an antibody response were considered. An increase in titer occurred in 90.7 per cent of those with initial levels of 100 units or less and in only 46.8 per cent of those with levels of 166 units or more.

Study of Type-Specific Agglutinins.—The development of agglutinins for the homologous Griffith type of hemolytic streptococci was studied



Antistreptolysin titers of 118 men with hemolytic streptococcus pharyngitis determined at the onset of the illness (lower dot) and during convalescence (upper dot). A simple dot indicates that no rash was present; a circled dot, that the subject had a rash. The lines of dashes indicate a fall in hemolysin titer.

by the slide technic in 118 of the cases. In 17 instances an increase in agglutinins occurred, the initial serums having given a negative reaction in every case. The final titers were approximately 1:3 in 10 cases, 1:12 in 5 and 1:24 in 2. These are believed to be significant changes. The average increase in antistreptolysin titer was somewhat greater in this group than among the patients in whose serum no agglutinins appeared. There was no apparent correlation between the development of these antibodies and the clinical course of the disease, but the number of cases was too small for detailed analysis.

TABLE 2.—*Relationship of Antibody Response to Initial Antistreptolysin Titer*

Initial Anti-streptolysin Titer	Total Subjects with Each Antibody Level	Average Final Anti-streptolysin Titer, Units	Ratio: Average Final Titer / Initial Titer	Number with No Response	Per Cent with No Response
25	8	168	6.7	1	12.5
50	21	222	4.4	1	4.8
100	25	211	2.1	3	12.0
125	17	310	2.5	4	23.5
166	17	345	2.1	9	52.9
250	18	360	1.4	9	50.0
333	8	328	0.99	5	71.5
500	4	522	1.05	2	50.0
Total	118			34	

COMMENT

The outbreak of hemolytic streptococcus tonsillitis described in this paper offered what may have been a unique opportunity to study certain features of group A hemolytic streptococcus antibody mechanics in human beings under con-

trolled conditions. The simultaneous infection of a large group of men of similar age by streptococci of a single type created an experiment which usually may be secured only in the laboratory in animals. The study of the antistreptolysin content of serums of 118 patients obtained during the acute stage of the illness and three weeks later, during convalescence, was instructive.

It is believed that the antibody titers of the serums obtained on the fourth day are comparable to those present at the onset of the infection. Experimental evidence [3] indicates that a demonstrable increase in the antistreptolysin or agglutinin titer of the serum rarely occurs before the seventh day following the onset of septic sore throat. Relatively few studies of antistreptolysin titers during the first week of such infections have been described, but the reports of Longcope [5] and Lippard and Johnson [6] tend to support this view.

Great differences in the amount of this antibody present initially were demonstrated, which permitted a correlation between these values and various features of the clinical disease. Those pertaining to the course of the illness and complications will be presented elsewhere. It was of interest to learn that there was no relationship between the initial level of antistreptolysin and that of the neutralizing antibody for the erythrogenic toxin, as expressed by lack of development of a rash.

It has been previously demonstrated [7] that the rash toxin is antigenically distinct from the labile toxins, of which the hemolysin is one, and this conclusion was amply confirmed in this study. It seems probable that several of these men, who had high antistreptolysin titers at the onset of their disease but in whom an erythema developed, had previously undergone infection by hemolytic streptococci which ineffectively formed erythrogenic toxin, so that high levels of antistreptolysin developed without the subject's becoming immune to the skin toxin.

Only a small number of the group had undergone tonsillectomy, and it was observed that these men had lower initial antistreptolysin titers than did the group as a whole. This tends to confirm the indication of the previous study [3] that the presence of hemolytic streptococci in the tonsils of carriers is associated with the maintenance of high levels of antistreptolysin. It was, of course, possible that these men were partially protected against infection by the absence of tonsils and had undergone less frequent and recent attacks of streptococcic disease.

Great differences in the magnitude of antistreptolysin response occurred. This is important, since such variation in the development of antibodies is commonly considered a factor of importance in recovery from various infections but has probably never before been demonstrated under controlled conditions in man.

The ratio of the final antistreptolysin titer to the initial titer varied inversely with the latter, since the patients having the lowest levels during the acute stage exhibited the greatest proportional response. No increase occurred in many men who had high titers at the onset. This indicates that there were definite levels of antibody above which further infection was unable to stimulate increase and that, if response occurred when large amounts of antibody were present, the relative magnitude of the reaction was much less than in the presence of small amounts.

An increased titer of agglutinins for the homologous type of streptococci developed in 14 per cent of the group, the titers being low. This is a less active response than has previously been shown to occur [2] following streptococcic tonsillitis, but it is a further demonstration of individual variation in antibody formation. The increase in antistreptolysin titer appeared to be greater in this group, but there was no correlation between the development of agglutinins and the clinical course of the disease.

SUMMARY

A large number of men of comparable age were simultaneously infected by a single type of group A hemolytic streptococci. Antistreptolysin and agglutinin titers in the serums of 118 of these men were measured at the onset of their disease and during convalescence. Great variation in the initial antistreptolysin titers was demonstrated. There was no correlation between the initial antistreptolysin titer and the presence of a rash. There was a relationship between the initial level and the absence of tonsils. Striking differences in the magnitude of antistreptolysin response were observed. These were closely correlated with the initial antibody titer. Fourteen per cent of the group acquired agglutinins for the homologous type of streptococci.

2398 Sacramento Street.

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THE OSCILLOMETRIC INDEX

AN AID IN EVALUATING THE ARTERIAL STATUS OF THE LOWER EXTREMITIES

CAPTAIN SEYMOUR H. RINZLER
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
JANET TRAVELL, M.D., AND HELEN CIVIN, M.S.
NEW YORK

The interpretation of the readings obtained by oscillometry in cases of arterial disease is rendered difficult by the number of factors which may influence the value at any single level of the extremities. For instance, the normal minimum reading at the ankle is given by various observers as ½,[1] 1,[2] 2 to 3 [3] and 3.[4] Because of these discrepancies, Atlas [5] compared the oscillometric reading at the ankle with that at the wrist and expressed the result in the form of a ratio. Since arteriosclerotic changes usually progress more rapidly in the lower than in the upper extremity, the reading at the wrist may be assumed to represent each patient's approximately normal value, and Atlas demonstrated that this oscillometric index (ankle/wrist) provides a better basis for evaluation of the arterial status in the leg than does an oscillometric reading at any single level of the extremity. In a series of 90 normal adults, Atlas [5a] found this ratio to be 1 or more, whereas in a series of 100 persons with arteriosclerosis of the lower extremities, the ratio was found to be less than 1. For these patients with low oscillometric indexes, the absolute oscillometric value proved misleading as a criterion of arterial disease of the extremities, since in half of them, despite the absence of pulsation in both the dorsal pedal and the posterior tibial arteries, the oscillometric reading at the ankle was 1 or more, which is generally accepted as normal. The oscillometric index, however, "enables the examiner to demonstrate in a roughly quantitative way decreased arterial pulsation in the lower part of the leg." [2b]

Our contribution to the problem is the correlation of Atlas' oscillometric index with other objective evidences of vascular disease, namely, results of cutaneous temperature tests and of roentgen examination of the vessels of the lower extremity. Such a correlation should indicate to what extent the oscillometric index of itself aids in evaluation of the arterial status of the lower extremities.

CLINICAL DATA

Oscillometric determinations were made at various levels, including the wrist, ankle and foot, on 84 ambulatory patients with heart disease. They were unselected with respect to their peripheral vascular status. These patients (63 men and 21 women), in addition to the oscillometric determinations, all had the following special examinations: (1) cutaneous temperature tests of the lower extremity following posterior tibial nerve block; (2) soft tissue roentgenograms of the lower extremities for evidence of calcification of the vessels, and (3) physical examination of the extremities for evidences of arterial insufficiency.

The cause of the heart disease was classified as follows: arteriosclerosis, 40 patients; hypertension, 2; hypertension and arteriosclerosis combined, 29; rheumatism, 6; hyperthyroidism and arteriosclerosis, 1; unknown, 6. The ages ranged from 35 to 80, with an average of 60 years. Results were excluded for patients in whom edema of the legs was present at the time of the oscillometric examination. There were no persons with thromboangiitis obliterans in the series.

TECHNICS

Oscillometric Index. — After exposing the arms to above the elbows and the legs to the knees, the patient rested in bed for ten minutes before the oscillometric readings were made. The Boulitte or the Collens oscillometer was used; identical readings were obtained with these two instruments. A cuff measuring 2 by 9 inches (5 by 23 cm.) was used; for the wrist and ankle readings it was applied so that its lower border reached the styloid and malleolar processes, respectively. The room temperature varied on different days from about 20 to 26 C. (68 to 78.8 F.).

From the Cardiac Service of Beth Israel Hospital.

1. Montgomery, H.; Naide, M., and Freeman, N. E.: The Significance of Diagnostic Tests in the Study of Peripheral Vascular Disease. Am. Heart J. **21**:780 (June) 1941.

2. (*a*) Samuels, S. S.: The Diagnosis of Peripheral Arterial Obstruction, J. Lab. & Clin. Med. **27**:19 (Oct.) 1941. (*b*) Atlas, L. A.: Oscillometry in Diagnosis of Arteriosclerosis of the Lower Extremities, Arch. Int. Med. **63**:1158 (June) 1939.

3. Bernheim, A. R., and London, I. M.: Arteriosclerosis and Thromboangiitis Obliterans, J. A. M. A. **108**:2102 (June 19) 1937.

4. Mufson, I.: Intermittent Limping: Intermittent Claudication; Their Differential Diagnosis, Ann. Int. Med. **14**:2240 (June) 1941.

5. Atlas, L. A: (*a*) Oscillometric Readings in Cases of Arteriosclerotic Disease of the Lower Extremity, Arch. Int. Med. **66**:155 (July) 1940; (*b*) footnote 2 *b*.

In calculating the oscillometric index, the average of the maximum readings obtained at the two wrists was used unless there was evidence of arterial obstruction in one arm due to thrombosis or embolism, in which case the ratio was calculated on the basis of the value obtained on the other arm. The figure obtained in this way was divided into the value for the ankle reading of that extremity on which a cutaneous temperature test had been done. In cases in which cutaneous temperature tests were available for both feet, the oscillometric index for each lower extremity was studied separately (10 cases); but since the oscillometric indexes were essentially the same for the two legs in each case, they were considered as one in the analysis of the data.

In order to test the constancy of the oscillometric index, the index was redetermined on 17 patients within six months after the original observations were made. We found that although the absolute oscillometric readings occasionally changed appreciably, the index usually remained remarkably constant and did not vary by more than 0.2 from the original value. For example, in 1 instance the initial average reading at the wrists was 2.5 and at the ankles 3.0, yielding an index of 1.20; five months later the reading at the wrists was 4.5 and at the ankles 5.5, yielding an index of 1.22.

TABLE 1.—*Comparison of the Results of Cutaneous Temperature Tests on the Same Extremity at Different Room Temperatures*

Patient	Date of Test	Room Temperature, C.	Maximum Cutaneous Temperature, C.	Change in Room Temperature, C.	Change in Maximum Cutaneous Temperature, C.
1	9/30/38	23.8	34.3		
	10/20/38	23.7	34.6	—0.1	+0.3
2	9/18/38	25.6	34.0		
	10/18/38	24.6	33.8	—1.0	—0.2
3	11/ 2/38	23.7	33.6		
	12/18/40	21.4	33.6	—2.3	0
4	10/ 3/38	23.8	31.2		
	11/29/38	21.4	31.3	—2.4	+0.1
	2/27/39	20.9	31.8	—2.9	+0.6
5	10/27/38	24.1	33.3		
	12/12/38	20.2	33.3	—3.9	0
6	10/ 3/38	26.6	32.1		
	10/12/38	23.3	31.9	—3.3	—0.2
	12/18/40	22.6	32.2	—4.0	+0.1
7	9/18/38	25.6	34.0		
	.....	20.4	33.5	—5.2	—0.5
8	8/17/38	32.5	33.9		
	.....	23.3	33.1	—9.2	—0.8
9	8/17/38	32.0	32.4		
	.....	21.0	32.7	—11.0	+0.3
10	8/17/38	31.2	33.5		
	.....	17.5	33.3	—13.7	—0.2
Average				—4.9	—0.04

Cutaneous Temperature Test.—To measure the radiation from the surface of the skin, the Hardy radiometer was used.[6]

During the course of any given cutaneous temperature test the room temperature was maintained practically constant. For different tests, however, the room temperatures ranged from approximately 20 to 26 C. (68 to 78.8 F.). It was demonstrated in another series of experiments that such differences in the room temperature did not influence the results (table 1 and chart 1). For one group of patients (patients 1 to 6) the cutaneous temperature test was repeated on the same extremity on different dates. For another group (patients 7 to 10) successive tests were carried out on the same day at different temperatures; an oxygen tent was used to secure the colder environment. It should be noted that results of duplicate tests at different temperatures varying as widely as 13 degrees (C.) (23.4 degrees [F.]) were not significantly different; for an average change of 4.9 degrees (C.) (8.8 degrees [F.]) in the environmental temperature, the average change in the vasodilatation temperature was negligible.

The procedure for the cutaneous temperature test was as follows: After exposing the legs to the knees, the patient rested in bed for fifteen minutes before the test was started. The temperature of the skin on the dorsal surface of the great toe of each foot was determined at intervals of five minutes until a constant level was reached or until the temperature of the toe began to decrease. This required from fifteen to forty minutes.

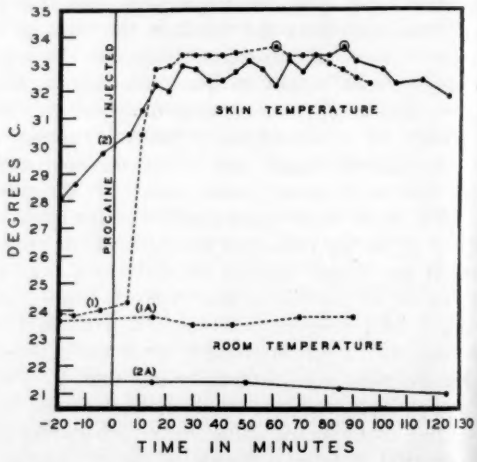

Chart 1 (table 1, patient 3).—Curve 1 shows the cutaneous temperature of the great toe after posterior tibial nerve block determined on Nov. 21, 1938, and curve 1 *A*, the room temperature during the test. Curve 2 shows the cutaneous temperature similarly determined on the same foot about one month later at a different room temperature, 2 *A*. Note that the same vasodilatation temperature (33.6 C. [92.5 F.]) was attained in both tests in spite of a difference of approximately 2 degrees (C.) in the room temperature. It is interesting that the oscillometric index in this instance was 0.27, despite the normal vasodilatation temperature.

Block of the posterior tibial nerve was then induced in one extremity by local infiltration with 10 cc. of a 2 per cent aqueous solution of procaine hydrochloride. The nerve block was judged satisfactory if there was loss of sensation to light touch on the dorsal surface of the big toe. Results for patients in whom the nerve block was judged incomplete were excluded. During the development of anesthesia, readings of cutaneous temperature were continued at five minute intervals until the readings obtained from the anesthetized toe

6. Hardy, J. H., and Soderstrom, G. F.: An Improved Instrument for Measuring Surface and Body Temperature, Rev. Scient. Instruments **8**:419, 1937. Hardy, J. H.: The Radiation of Heat from the Human Body, J. Clin. Investigation **18**:593 (July) 1934.

had reached and passed a peak, as indicated by declining values. The results of two typical tests are shown in chart 1.

To ascertain the normal vasodilatation temperature under these conditions, we examined 14 patients who were under 35 years of age (average 25 years) and who had mitral valvular disease without clinical evidence of vascular disease of the extremities. In this group the maximum cutaneous temperature after blocking of the posterior tibial nerve ranged from 32.7 C. to 34.7 C (90.8 to 94.7 F.), with an average of 33.7 C. (92.7 F.). These results suggest that a value of less than about 32.5 C. (90.5 F.) may be abnormal. This is in harmony with the figure 32 C. (89.6 F.) taken by Gibbon and Landis as representing the lower limit of the normal vasodilatation temperature determined under somewhat different conditions.[7]

CORRELATION OF THE OSCILLOMETRIC INDEX WITH OTHER TESTS OF ARTERIAL DISEASE

For analysis, the 84 subjects who form the basis of this study were divided arbitrarily into several groups according to the oscillometric index: those with an index of 1.0 or more; those with indexes of 0.99 to 0.75, 0.74 to 0.51 and 0.50 to 0.31 and those with an index of 0.30 or less. It may be seen in table 2 that these groups are essentially comparable with respect to age, sex and incidence of hypertension. The incidence of diabetes mellitus, however, is appreciably higher for the groups with an oscillometric index below 0.51.

A correlation of the oscillometric index with the data secured by other means of examination shows (table 2), first, that the groups with an index of 1.0 or more and the one with an index of 0.75 to 1.0 are essentially similar and, secondly, that as the oscillometric index falls below 0.75, the per cent of subjects with abnormal findings by roentgen examination and cutaneous temperature studies increases. This suggests that a value of 0.75 may be regarded as the lower limit of normal, rather than an index of 1.0 as stated by Atlas.[2b]

Calcification, it may be noted (table 2), occurs in 37 to 40 per cent of the patients having a normal oscillometric index. When the index falls below 0.75, the incidence of calcification of the arteries of the lower extremities approximately doubles; when the index falls below 0.51, calcification occurs in 100 per cent of the patients. It is noteworthy that not only the incidence but the extent of calcification increases as the index falls.

The cutaneous temperature test shows a normal average value (33.0 C. [91.4 F.] or more) until the oscillometric index falls below 0.31, when the vasodilatation temperature declines to an average of 31.8 C. (89.2 F.) (table 2).

TABLE 2.—*Correlation of the Oscillometric Index with Other Laboratory and Clinical Data*

Oscillometric Index	No. of Cases	Male, per Cent	Average Age (Range), Yr.	Diabetes, per Cent	Hypertension, per Cent	Maximum Cutaneous Temperature After Nerve Block: Average (Range), C.	Maximum Cutaneous Temperature After Nerve Block: 32.5 C. or Less, per Cent	Maximum Cutaneous Temperature After Nerve Block: 31.5 C. or Less, per Cent	Calcification,* per Cent	Absence of Pulsations,† per Cent	Zero Oscillometric Reading at Foot, per Cent
1.0 or more	33	64	59 (36-76)	15	60	33.2 (31.8-35.9)	13	0	37	0	0
0.99-0.75	20	75	57 (35-73)	5	60	33.4 (31.9-35.6)	15	0	40	0	0
0.74-0.51	11	82	57 (42-80)	9	64	33.0 (32.2-34.0)	27	0	73	0	0
0.50-0.31	7	85	61 (43-70)	43	71	33.2 (31.9-34.7)	28	0	100	43	29
0.30 or less	13	85	62 (50-77)	30	77	31.8 (30.3-33.6)	77	38	100	62	30

* Vessels of the lower extremities.
† Pulsations absent in both dorsal pedal and posterior tibial arteries.

Since there is some disagreement in the literature as to what constitutes the lower limit of the normal vasodilatation temperature, the data were analyzed with respect to the per cent of subjects having values below both 32.5 and 31.5 C. (90.5 and 88.7 F.). With use of either of these figures, it may be seen that the most striking rise in the incidence of abnormal cutaneous temperatures occurs when the oscillometric index falls below 0.31. It should be noted, however, that in this lowest range of the oscillometric index, the vasodilatation temperature was normal in 3 instances. A correlation of the oscillometric index with the vasodilatation temperature is shown in chart 2.

In the case of the clinical examination, the incidence of absence of pulsations on palpation of the dorsal pedal and posterior tibial arteries increases sharply when the oscillometric index falls below 0.51; this fact is substantiated by a similar observation with respect to the incidence of a zero oscillometric reading at the foot (table 2). For the group of subjects with an

7. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, J. Clin. Investigation **11**:1019 (Sept.) 1932.

oscillometric index in the lowest range (below 0.31), the clinical diagnosis was arteriosclerosis obliterans. These patients all had physical signs of arterial insufficiency, including pallor on elevation and rubor on dependency; 6 had intermittent claudication, but in all the subjects physical

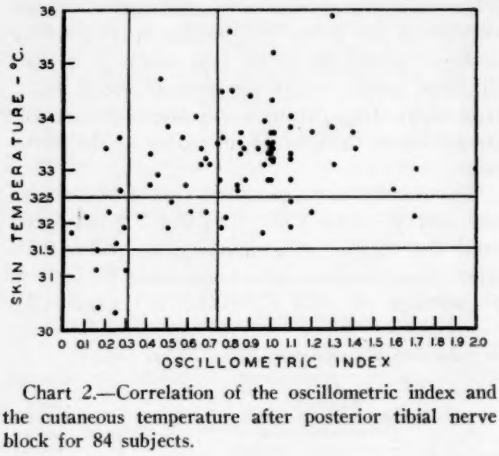

Chart 2.—Correlation of the oscillometric index and the cutaneous temperature after posterior tibial nerve block for 84 subjects.

activity was limited by a low cardiac reserve. All had extensive calcification on roentgen examination. The cutaneous temperature test confirmed the presence of occlusive arterial disease in 10 of the 13 subjects; in these 10 the vasodilatation temperature ranged from 30.3 to 32.2 C. (86.5 to 90 F.), with an average reading of 31.4 C. (88.5 F.); in the other 3 subjects, the vasodilatation temperatures were 33.6 (92.5 F.) (duplicate readings on 2 tests as shown in chart 1), 33.4 (92.1 F.) and 32.6 (90.7 F.), respectively.

The finding of a normal vasodilatation temperature together with a low oscillometric index is perhaps surprising. A possible explanation is that the lowering of the oscillometric index for these persons is the result of an extremely inelastic vessel wall due to heavy calcification of one or more large arteries in the leg, while the relatively nonpulsatile arterial flow through the pipestem vessel remains adequate. Another possibility is that adequate collateral circulation has been established in the foot after occlusion of a section of one of the larger arteries above the ankle; the development of adequate collateral flow under these conditions has been demonstrated by means of arteriography.[8] In view of the positive clinical signs of arterial insufficiency in these subjects, it appears that occasionally the oscillometric index may be a more reliable guide to the presence of arteriosclerosis in the lower extremity than is the cutaneous temperature test.

The data were analyzed to determine whether a single oscillometric reading at the foot or ankle would yield as much information regarding the arterial status as does the oscillometric index. Chart 3 shows that in general there is a correlation of the ankle reading with the oscillometric index. Thus, no patient with an ankle reading above 4.0 had an oscillometric index below 0.75, and no patient with an ankle reading of less than 1 had an oscillometric index above 0.3 or a vasodilatation temperature above 32.5 C. (90.5 F.). However, it may be seen that for ankle readings between 1 and 4 the oscillometric index and the vasodilatation temperature vary widely, yielding both normal and abnormal values; hence an ankle reading which falls in this range must be regarded as ambiguous. A comparison of the oscillometric reading at the foot with the oscillometric index (table 3) similarly shows that oscillometric readings at the foot which fall in the range of ⅛ to 2 are ambiguous, since the oscillometric index for these patients varied from 0.3 or less to 0.75 or more. However, no patient with a reading at

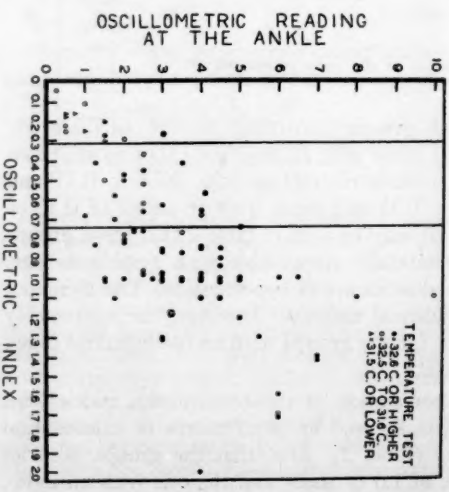
OSCILLOMETRIC READING AT THE ANKLE
0 1 2 3 4 5 6 7 8 9 10
OSCILLOMETRIC INDEX
TEMPERATURE TEST
32.6 C. OR HIGHER
32.5 C. TO 31.6 C.
31.5 C. OR LOWER

Chart 3.—Correlation of the oscillometric index, the oscillometric reading at the ankle and the cutaneous temperature after posterior tibial nerve block for 84 patients.

the foot of more than 2 had an index less than 0.75, and no patient with a zero oscillometric reading at the foot had an oscillometric index above 0.3. It is apparent that the oscillometric

8. Yates, W. W.: Maintenance of the Functional Integrity of Occluded Large Arteries as Demonstrated by Thorotrast Arteriography, Am. J. M. Sc. **194**:372 (Sept.) 1937.

index is, in general, more useful in evaluating arteriosclerosis of the lower extremity than is the oscillometric reading at the foot or ankle when the latter readings fall within these intermediate ranges.

SIGNIFICANCE OF OBJECTIVE TESTS IN CASES OF ARTERIOSCLEROSIS OF THE LOWER EXTREMITY

The data were next analyzed to answer, if possible, certain questions relating to the life history of arteriosclerosis in the lower extremity and to criteria for the diagnosis of this condition: First, which of these objective tests—the soft tissue roentgenogram, the oscillometric index and the cutaneous temperature test—yields the earliest clue to the existence of arteriosclerosis in this part of the body; second, how often does each test provide the sole evidence of arteriosclerosis, and, third, can any one test alone be relied on to establish this diagnosis?

TABLE 3.—*Comparison of the Oscillometric Reading at the Foot with the Oscillometric Index*

Oscillometric Index	Total No. of Cases	Oscillometric Reading at the Foot: 0 Per cent	½ to ½ Per cent	⅝ to 1 Per cent	1⅛ to 2 Per cent	2⅛ or More Per cent
0.75 or more	53	0	34	30	29	7
0.74 to 0.31	18	11	40	39	10	0
0.30 or less	13	30	46	24	0	0

It is apparent that roentgen examination usually affords the earliest evidence of this condition, for calcification of the vessels was noted in about 38 per cent of the group with a normal oscillometric index. None of these 20 patients with calcification had clinical evidence of arterial insufficiency, and the vasodilatation temperatures were also normal, except possibly in 2 instances (32.2 and 32.1 C. [90 and 89.8 F.], respectively). Excluding these 2, calcification was the sole abnormality demonstrable by these three tests in 21.4 per cent of the series of 84 subjects.

A low oscillometric index was the sole abnormality in 2 of the 11 subjects for whom the index fell in the intermediate range of 0.74 to 0.51, or in approximately 2.4 per cent of the series of 84 subjects. In 1 additional instance an oscillometric index of 0.62 was associated with a vasodilatation temperature of 32.2 C. (90 F.). When the oscillometric index was 0.5 or less, calcification was always present and frequently a low vasodilatation temperature and clinical signs of arterial insufficiency were noted.

When the vasodilatation temperature was in the lowest range, below 31.5 C. (88.7 F.), all other methods of examination which were employed revealed arterial disease of the lower extremities. However, the cutaneous temperature test was the only objective technic suggestive of such pathologic change in 3 of the 12 subjects with vasodilatation temperatures below 32 C. (89.6 F.) and in 5 of the 22 subjects with vasodilatation temperatures below 32.5 C. (90.5 F.). These figures represent 3.5 and 6.0 per cent respectively of the series of 84 subjects.

Thus at the two extremes were the group (18 subjects) with minimal functional changes, in whom the vascular examination revealed nothing abnormal except calcification, and the group (20 subjects) with advanced arterial insufficiency, in whom several or all of the tests yielded abnormal results. In an intermediate group (46 subjects) we should have been uncertain as to the existence of arterial disease except for the oscillometric index in 2 instances (4.3 per cent) and the vasodilatation temperature (below 32.5 C.) in 4 (10.9 per cent). The soft tissue roentgenogram seems to be the most reliable, though not an infallible, technic for the detection of the mere presence of arteriosclerosis, but no single test can be relied on to establish this diagnosis in all cases. Judgment as to the course of arteriosclerosis or the degree of occlusive disease ideally should be based on examinations which include determination of both the oscillometric index and the vasodilatation temperature.

PRACTICAL VALUE OF THE OSCILLOMETRIC INDEX

In evaluating the usefulness of the oscillometric index, one should consider the test in relation to several diagnostic problems. The first of these is how to distinguish intermittent pain in the lower extremity which is of nonvascular origin from that which is due to arterial insufficiency. As Mufson [4] has pointed out, the differentiation of intermittent limping due to orthopedic or neurologic changes from intermittent claudication due to peripheral vascular disease presents many difficulties; he noted, however, that "an equally normal oscillometric reading on both legs is the most dependable sign of a competent peripheral vascular system." Since our data show that the oscillometric index is a more reliable guide to arterial function than is the absolute oscillometric reading at either the foot or the ankle, it would follow from this statement that the oscillometric index is the most useful single technic to determine whether the pain is or is not due to arterial insufficiency.

In the presence of a normal oscillometric index, one may be assured that this symptom is not due to arteriosclerosis.

The second problem is as follows: Given a patient with arteriosclerosis and arterial insufficiency of the lower extremities, how may one discover what role the factor of spasm and what role the factor of organic narrowing of the lumen plays in the occlusive process? The cutaneous temperature test after nerve block yields the final answer to this question. Our data show, however, a close, although not perfect, correlation between the results of the cutaneous temperature test and the level of the oscillometric index. Thus, a small proportion (13 per cent) of the subjects with a normal index (0.75 or more) had vasodilatation temperatures within the borderline range of 32.5 to 31.5 C. (90.5 to 88.7 F.) and none had a cutaneous temperature below 31.5 C. (88.7 F.), whereas nearly half of the patients with a very low index (0.3 or less) had a vasodilatation temperature in this borderline range and in one third the cutaneous temperature was below 31.5 C. (88.7 F.). Such a correlation is to be expected, because the lower extremities are usually affected by arteriosclerosis earlier and to a greater degree than are the upper extremities; this fact has been particularly well demonstrated by Sappington and Horneff by means of microscopic comparisons of the tibial and radial arteries for the different decades of life.[9] Because of the general parallelism between the oscillometric index and the cutaneous temperature after nerve block, a fairly reliable judgment can be made by means of the former, simpler, technic as to the relative roles played by organic occlusive disease and by functional spasm in the production of arterial insufficiency.

A third problem relates to the evaluation of the arterial status in a patient who is found by roentgenogram to have calcification of the vessels of the lower extremities. The incidence of this abnormality in the absence of symptoms is perhaps surprisingly high. Thus Sappington and Horneff[9] reported that sections of the tibial artery showed calcification in 37 per cent of a group of patients 41 to 60 years of age presenting no definite signs of arterial obstruction in the extremities. This figure is in close agreement with the 38 per cent incidence of calcification observed by roentgenogram in our series of 53 patients of similar age and with an oscillometric index above 0.75; these patients also showed no evidence of arterial insufficiency. How this situation arises has been explained by Hines and Barker[10]: "In arteriosclerosis obliterans, calcification and other forms of degeneration of the medial coat have no clinical significance in themselves, inasmuch as they do not cause significant interference with the flow of blood. The important component of the lesion present in arteriosclerosis obliterans seems to be the atheromatous plaque, because this is responsible in itself for partial occlusion of the lumen, and it is the locus for the development of the thrombus which completes the occlusion." Since in our series lowering of the oscillometric index below 0.75 is associated with a progressive increase in the incidence of calcification up to 100 per cent for the lowest indexes and with an increase in the incidence of abnormal cutaneous temperatures, an abnormal oscillometric index may be taken to indicate that the atheromatous occlusive process is being superimposed on the medial calcification. Thus it appears that the level of the oscillometric index provides a satisfactory guide to the degree of the occlusive process even in the presence of calcification of the vessels.

SUMMARY AND CONCLUSIONS

The oscillometric index (ratio of the oscillometric reading at the ankle to that at the wrist), the cutaneous temperature following posterior tibial nerve block and the presence or absence of calcification of the vessels of the lower extremities in the roentgenogram were determined for 84 ambulatory patients with heart disease.

A correlation of the data obtained by these three laboratory aids (oscillometry, cutaneous temperature test and soft tissue roentgenogram) shows that as the oscillometric index decreases the incidence and extent of calcification of the vessels of the lower extremity and the incidence of abnormal cutaneous temperatures increase.

In the presence of a normal circulation in the upper extremity, an oscillometric index of 0.75 or more almost always indicates adequate arterial function in the lower extremity. Similarly, an index of less than 0.75 indicates sclerotic changes in the arteries of the leg, probably with calcification, and an index of 0.3 or less indicates extensive calcification and probably advanced occlusive arterial disease.

9. Sappington, S. W., and Horneff, J. A.: Tibial Artery Changes in Comparison with Those of the Radial and Coronary Arteries, Am. J. M. Sc. **201**:862 (June) 1941.

10. Hines, E. A., Jr., and Barker, N. W.: Arteriosclerosis Obliterans: A Clinical and Pathological Study, Am. J. M. Sc. **200**:717 (Dec.) 1940.

The oscillometric index is of greater value in estimating the presence and degree of arteriosclerotic disease in the lower extremity than is the oscillometric reading at the foot or ankle when the latter readings fall within an intermediate range of about 1 to 4 at the ankle and ⅛ to 2 at the foot.

An oscillometric reading of more than 4 at the ankle or more than 2 at the foot nearly always indicates normal arterial flow, and a reading of less than 1 at the ankle or 0 at the foot indicates occlusive arterial disease.

Roentgen examination for calcification of the vessels usually affords the earliest evidence of arteriosclerosis of the lower extremities.

Final appraisal as to the degree of occlusive arterial disease of the lower extremities ideally should be based on examinations which include determination of both the oscillometric index and the vasodilatation temperature.

Duplicate determinations of cutaneous temperature on 10 patients showed that a variation of several degrees (C.) in the room temperature does not materially influence the vasodilatation temperature after posterior tibial nerve block.

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1943

FRANCIS M. RACKEMANN, M.D.
Lecturer in Medicine, Harvard Medical School; Physician, Massachusetts General Hospital
BOSTON

ALLERGY IN THE ARMY

The Army is cautious about accepting selectees who give evidence of having hay fever, asthma or eczema, and this is proper. The symptoms carry a potential risk of later disability which is often considerable, and so far the methods of dealing with these allergic states are not developed as well as they might be in the Army.

In the First Army Corps Area, Hyde and Kingsley [1] made a study of the incidence of allergy among the registrants at the induction center. There were 60,000 registrants, and of these 21,500 were rejected. Allergy, however, was the cause of less than 1 per cent of the rejections. There were only 495 rejections on account of allergy, and most of these were for asthma. It is interesting that there were only 11 men with eczema and 12 with dermatitis in this large group. Incidentally, the officers reviewed the social classification of the rejected men and found that almost twice as many allergic persons came from the semirural districts as came from the crowded tenement areas. It looks as though allergy were a disease of the country more than of the city.

After selection has been accomplished and training begun, the incidence of allergy appears to increase, and it is higher in this war than it was in World War I. In 1918, only 5 men per hundred thousand were discharged from the Army because of asthma, but from June 1, 1941 to Oct. 1, 1942 Blank [2] saw 1,833 patients in the allergy clinic in Fort Eustis, and 78 of these, or 4 per cent, were given disability discharges, all but 3 because of asthma. More recently, Colonel French and Major Halpin [3] have shown what can be done by increasing the knowledge and interest in allergy in one service command. With an expenditure of less than $500 they were able to supply testing and treatment materials to 59 different clinics in the Fourth Corps Area. In each station hospital an allergy clinic was organized and the personnel were given special instruction. The result is interesting: Since March 1942, 3,419 Army and 498 civilian patients have been treated. Of these, 1,153 were admitted to the hospital, to stay an average of eighteen and one-tenth days. Of the 3,419 Army patients, 195, or 6 per cent, were discharged from the service, about the same proportion as in Blank's series. On the other hand, 267 men were reclassified and retained in the service. In this series hay fever without asthma accounted for 1,269 cases, while asthma was present in about 1,000. Meantime there were 350 cases of urticaria, 79 of migraine and 138 of eczema. All these figures look large until one considers what might be the total number of men in the Fourth Corps Area. In the *Massachusetts General Hospital News* is an interesting letter which states that in a base hospital in North Africa asthma stood third in the list of medical disabilities (psychic disorders were first; gastrointestinal disease was second, and asthma was third).

It is evident that the problem of allergy is of practical importance in the Army in spite of the effort to eliminate persons who present "significant" symptoms of it. It is to be hoped that the authorities will recognize the accomplishments of Colonel French and will consider better methods, first of recognition and elimination and then of treatment, in case the elimination of this troublesome group of disabilities has not been successful.

HAY FEVER

Hay fever is still an open problem. There are a few advances this year but not enough. Loveless has continued her studies on the blocking antibody. Last year she [4] made an interesting study on 3 normal volunteer subjects treat-

1. Hyde, R. W., and Kingsley, L. V.: Distribution of Allergic States in Selectees, J. Allergy **14**:386, 1943.

2. Blank, P.: Military Aspects of Allergy, J. Lab. & Clin. Med. **28**:609, 1943.

3. French, S. W., and Halpin, L. J.: Army Allergy: Report on Allergy Clinics in the Fourth Service Command, Ann. Allergy **1**:1, 1943.

4. Loveless, M. H.: Immunological Studies of Pollinosis: III. Fluctuations in Antibody-Titer of Normal Individuals Subcutaneously and Intravenously Injected with Pollen Extract Over Protracted Periods, J. Immunol. **44**:1, 1942.

ing them with large doses of pollen extract given at intervals for several months. The blocking antibody was produced in higher concentration by treatment with alum-precipitated (particulate) ragweed than by injections of clear solutions. Also she found that when an extra dose was given after a rest period of several months the concentration of the blocking antibody increased rapidly and to a high level. This result suggests that the perennial method of treating hay fever with doses given at intervals of several weeks throughout the year ought to be more effective than the more conventional preseasonal method. This year in a study reported in a paper read before the American Society for the Study of Asthma and Allied Conditions, Dr. Loveless [5] has shown that the titer of the blocking antibody varies in accordance with the symptoms of the patient. She believes that the relief from symptoms depends on the development of this particular antibody.

Hampton and co-workers [6] in Dr. H. L. Alexander's clinic at Washington University in St. Louis, have developed a method of detecting the thermostable antibody by a precipitin reaction. Rabbits are inoculated with a suspension of ragweed proteins precipitated by aluminum hydroxide cream, and the resulting immune serum is used to test the excess of ragweed which may remain when the patient's serum is mixed with small quantities of ragweed. If the union between serum and ragweed is firm, no excess results, and there is nothing which blocks the reaction; but if, on the other hand, an excess of ragweed can be demonstrated, one can say that not all the ragweed has been combined. The method deserves further study. Frank and Gelfand [7] looked for blocking substances effective for ragweed in other kinds of serum. They found, however, that convalescent scarlet fever serum was unable to inhibit the union of ragweed antibodies with the antigen and that the serum from patients with pneumonia or measles was likewise ineffective.

These researches are important, but one should bear in mind that in hay fever it is the sessile cellular antibodies which are of particular importance. Dr. R. A. Cooke once asked me whether the Widal reaction (a test for antibodies) was a true index of immunity from typhoid fever!

There are other studies of antibodies which do not refer directly to ragweed but which are nevertheless of interest. Kulka [8] found that antigen-antibody mixtures (antipneumococcus serum with specific polysaccharide) fail to stimulate a strip of isolated muscle unless an excess of free antibody is present. Hansen-Pruss and Raymond [9] found that the serum of allergic women contains the highest rate of reagin titer on the last day of menstruation. This titer is in inverse proportion to the level of estrogen. On the other hand, Von Haam and Rosenfeld [10] observed that estrone produced a remarkable increase in specific antibodies when it was given to both castrated and noncastrated rabbits of both sexes previously treated with pneumococcus vaccine.

The question of the specificity of the ragweed antigen is of great practical importance. Simon [11] studied the allergenic relationship between the pollens of dwarf and giant ragweed and several of their botanic relatives. First he found that of 40 patients sensitive to the ragweeds 38 reacted to skin tests with other compositae. Serum from 6 of these was mixed with extracts of various pollens, and then the mixture was injected into the skin of nonsensitive recipients. Later the prepared sites were tested with other extracts. The question was whether the allergy resulted from exposure to each species separately or whether the multiple sensitiveness shown by skin tests could be explained on a basis of "crossed reactions." In 4 of the 6 cases dwarf ragweed could have been the only sensitizing agent, for none of the other pollens could neutralize the antibodies for this ragweed. In none of the 6 could cosmos, sunflower, goldenrod or dandelion have been the only sensitizing allergen. Simon's experiments show that the pollens of ragweed and their botanic relatives contain multiple common allergic determinants as well as species-specific allergens. Different persons exposed to this

5. Loveless, M. H.: Immunological Studies of Pollinosis: IV. The Accelerated Immune Response in Hay Fever Patients, read before the American Society for the Study of Asthma, New York, Dec. 5, 1942.

6. Hampton, S.; Johnson, M. C.; Alexander, H. L., and Wilson, K. S.: Detection of the "Thermostable" Antibody by Means of the Precipitin Reaction, J. Allergy **14**:227, 1943.

7. Frank, D. E., and Gelfand, H. H.: Studies on the Blocking Antibody in Serum of Ragweed-Treated Patients: I. A Search for Inhibiting Substances in Other Types of Immune Serum, J. Allergy **14**:273, 1943.

8. Kulka, A. M.: Studies on Antibody-Antigen Mixtures: II. The Effect on Normal Living Excised Tissue and Its Dependence on the Presence of Free Antibody in the Mixture, J. Immunol. **46**:235, 1943.

9. Hansen-Pruss, O. C., and Raymond, R.: Influence of the Menstrual Cycle on the Titer of Circulating Allergens, J. Clin. Endocrinol. **3**:81, 1943.

10. Von Haam, E., and Rosenfeld, I.: The effect of Estrone on Antibody-Production, J. Immunol. **43**:109, 1942.

11. Simon, F. A.: Allergenic Relationship of the Pollens of Dwarf and Giant Ragweed to Several of Their Botanic Relatives, J. Exper. Med. **77**:185, 1943.

group of pollens may become sensitized to one or more members in one case and to other members in other cases. Specificity is present, but crossed relationships are frequent and important.

Pollen Chemistry.—This is important, because the chemical mixtures which constitute routine extracts cause effects which are always hard to interpret. Abramson, Engel and Moore [12] have continued their electrophoretic analyses of pollen. In timothy pollen there is a major component which moves slowly in the electrical field and is colorless, but in addition there are at least six other components which are negatively charged and are pigmented. It is important to note that each one of these fractions elicits a positive reaction in skin tests on sensitive patients.

Cohen and Friedman [13] tried to extend Stull's experiment in which "fraction I" was split off from the crude ragweed extract by half saturating the solution with ammonium sulfate. By a combination of ammonium sulfate precipitation, dialysis, and freezing and thawing, they obtained a purified globulin which appeared to react specifically with its own reagin. They were able to produce crystals which were highly active in direct skin tests and which had a high neutralizing capacity as tested on rabbit antiragweed serum. It looks as though Cohen and Friedman had arrived at a fairly pure product.

Harsh and Huber [14] digested the extract of giant ragweed pollen with freshly assayed pancreatin and also with highly active pepsin. The skin test activity of the digest was greatly reduced, but, on the other hand, it was not eliminated entirely.

Finally, Newell,[15] working in the laboratory of physical chemistry at the Harvard Medical School, through the courtesy of Professor Cohn, used ample quantities of materials with good technic and was able to separate what appeared to be a number of separate fractions from the crude ragweed material. Some of these were obtained by concentrated phosphate buffers, others by precipitation with ethyl alcohol and still others by precipitation with ammonium sulfate. Each of these fractions was then studied in the Tiselius apparatus so that the electrophoretic pattern could be determined. Whereas single peaks in the record of the movement of various protein components might indicate a substance of single chemical purity, multiple peaks demonstrate that several different substances are present. Newell found that without exception each of the fractions which he had prepared so carefully was "contaminated"; none of them showed a single peak; each of them gave evidence of the presence of some other substance besides the fraction desired. Whereas this work of Newell is not exactly constructive, at least it demonstrates that up to the present time there is no method known by which a pure chemical fraction from ragweed can be obtained.

Pollen Surveys.—Pollen surveys are interesting. Vaz-Ferreira and Recarte [16] review the allergenic flora of Uruguay. The methods for describing the content of pollen in the air are reviewed by Dahl and Ellis,[17] who recommend that reports include the actual findings, namely, the amount of pollen per unit of area on the slide exposed. The idea has the advantage of simplicity, but still the data will have to be expressed in such a way as to make it easy to compare them with those of other workers.

Molds.—That the spores of molds are responsible for the symptoms in many obscure cases of hay fever, especially when the reactions to skin tests remain negative, is becoming more and more evident. More studies of molds and of the reactions which they produce are needed. Browning [18] has made a practical study of skin tests with molds on a series of allergic patients as well as on normal persons. Thirty-eight different mold extracts were used—different strains from the genera Alternaria, Aspergillus, Hormodendron and Penicillium. From 800 to 1,400 subjects were tested with representatives of each genus, and positive results were obtained in about 25 per cent of the group as a whole. About one third of the mold extracts were too irritating to be of diagnostic importance; the other two thirds gave satisfactory readings, but only a few seemed to have real diagnostic importance.

In the discussion of Browning's paper, Feinberg stated that of 253 patients who had a his-

12. Abramson, A.; Engel, M. G., and Moore, D. H.: Skin Reactions to Electrophoretic Fractions of Timothy and Pollen Extract, J. Allergy **14**:65, 1942.

13. Cohen, M. B., and Friedman, H. J.: Preliminary Report on the Fractionation of Ragweed Pollen and Immunologic Studies with These Fractions, J. Allergy **14**:368, 1943.

14. Harsh, G. F., and Huber, H. L.: Studies of Tryptic and Peptic Digestion of Extracts of Giant and Ragweed Pollen, J. Allergy **14**:121, 1943.

15. Newell, J. M.: Electrophoretic Studies on the Chemical Fractionation of Ragweed Pollen Extracts, J. Allergy **14**:444, 1943.

16. Vaz-Ferreira, R., and Recarte, P.: Allergenic Flora of Uruguay, Arch. Soc. de biol. de Montevideo **10**:274, 1942.

17. Dahl, A. O., and Ellis, R. V.: The Pollen Concentration of the Atmosphere, Pub. Health Rep. **57**: 369, 1942.

18. Browning, W. H.: Mold Fungi in the Etiology of Respiratory Allergic Diseases, J. Allergy **14**:231, 1943.

tory suggesting allergy to molds 241 gave positive reactions to skin tests with molds, whereas of 351 patients whose history did not suggest sensitivity to molds only 10 had positive readings.

Kurung [19] isolated and identified the fungi in sputum. His paper contains a number of beautiful pictures to show the technic and the results.

ASTHMA

Physiology and Pathology.—In my review of the literature on allergy for the year 1941 [20] I presented a table which showed that the symptom asthma could be caused by various lesions. Spasm and edema of the bronchial mucous membrane constituted one cause; exudate in the tubes, another; obstruction by a foreign body or by a tumor, a third; emphysema, a fourth, and passive congestion in heart disease, a fifth.

At a meeting of the Association for the Study of Allergy in June 1942, Lamson read a paper by Lamson, Butt and Stickler [21] reviewing the pathologic observations in 86 cases in which asthma was given as either the primary or the secondary cause of death. The patients included 25 women, 57 men and 4 children. Of the 86 patients, 24 died primarily of heart disease and had asthma as a secondary diagnosis. Three of them had syphilis, 4 had pneumonoconiosis and 3 died of morphinism. Cancer and tuberculosis were included among other miscellaneous diagnoses. This paper shows well that asthma must be regarded as a symptom and not as a disease. On the other hand, there is good evidence that death can be produced by asthma without other cause, and in such circumstances the pathologic picture is typical. The group studied by Lamson and his associates includes 11 patients in whom the autopsy revealed the presence of tough sticky plugs which occluded the larger and medium-sized bronchi to make a characteristic picture of death by suffocation from asthma itself. One should note, however, that 24 is only about 28 per cent of the total group.

In children, Cohen [22] has found again that a clinical picture which simulates that of bronchial pneumonia may depend on the formation of tenacious plugs which become more tenacious when excessive vomiting leads to dehydration and which may occlude a bronchus to produce atelectasis and a low grade pneumonitis in the distal portions. Occasionally bronchoscopy is indicated, but so far it is his experience that the prognosis is good and recovery occurs.

Ayerza's disease is described by Fernandes Pontes and co-workers [23] from the University of São Paulo, in Brazil, as due to a chronic obstructive bronchial pulmonary emphysema. The cyanosis indicates a lack of oxygen in the blood, and this anoxia stimulates the bone marrow to increase its activity with resulting polycythemia. The authors describe 2 cases in which bronchitis had lasted for forty and twenty-two years respectively but the severe dyspnea and cyanosis had been present for only a few months. This is interesting because we have been led to believe that Ayerza's disease is dependent in most cases on lesions of the pulmonary vascular system rather than of the lungs and bronchi.

More observations are needed on the condition of the cilia in the epithelium of the trachea and larger air tubes. Hilding [24] recalls that in the influenza pandemic of 1918 the autopsies on many patients showed the cilia to be destroyed. Now he describes a group of patients who died from asthma and other respiratory diseases in whom rather typical changes in the epithelium of the larger air passages were observed. In 12 patients large goblet cells were substituted for the normal columnar ciliated cells. In 11 the cilia were lost and the bronchi were filled with purulent secretion somewhat as described in Lamson's series. These patients also died of suffocation. Five patients had bronchial constriction without change in the epithelium. One patient died in extreme distress from a severe tracheobronchitis; in his case the ciliated epithelium had all disappeared and in addition all the bronchi were filled with viscid plugs. As Hilding suggests, it is easy to conceive of a profound disturbance in the normal mechanism by which pulmonary secretions and exudate are removed by the cilia and so to consider how dry sticky plugs can be formed.

Cralley [25] studied the ciliary action of the tracheal tree in rabbits. He placed his animals

19. Kurung, J. M.: The Isolation and Identification of Pathogenic Fungi from Sputum, Am. Rev. Tuberc. **46**:367, 1942.

20. Rackemann, F. M.: Allergy: A Review of the Literature of 1941, Arch. Int. Med. **69**:128 (Jan.) 1942.

21. Lamson, R. W.; Butt, E. M., and Stickler, M.: Pulmonary Pathology with Special Emphasis on Bronchial Asthma, J. Allergy **14**:396, 1943.

22. Cohen, S.: Allergic Respiratory Disease and Pneumonia in Childhood, New Orleans M. & S. J. **94**:440, 1942.

23. Fernandes Pontes, J.; Jamra, M., and Carvalho da Silva, A.: Cyanotic Chronic Bronchopneumopathy: Clinical and Physiopathologic Study, An. Fac. de med. da Univ. de São Paulo **16**:365, 1940.

24. Hilding, A. C.: The Relation of Ciliary Insufficiency to Death from Asthma and Other Respiratory Diseases, Ann. Otol., Rhin. & Laryng. **52**:5, 1943.

25. Cralley, L. J.: Factors Affecting Retention and Rate of Removal of Bacteria from the Tracheal Tree and Lungs, Am. J. Hyg. **36**:303, 1942.

in a closed chamber and sprayed them with bacteria, and then he made changes in temperature and humidity to see if he could influence the rate at which the foreign substance was removed from the lungs. He found that the normal ciliary function was very effective and it was only when the temperature and humidity were modified to extreme degrees that it was disturbed.

When asthma depends on the retention of sticky material in the bronchi, one understands why bronchoscopy should be advocated. Friedberg [26] reviews the literature and describes the cases of 8 patients who were relieved by bronchoscopy. Four of them, however, were small children in whom the removal of a foreign body removed the asthma also. Patient 5 was a woman who had a broncholith which acted as a foreign body. Patient 6 had a pulmonary abscess, and patients 7 and 8 had stenosis of a bronchus, in 1 of them due to tuberculosis. It is a little disconcerting not to find any of the cases with the pathologic changes which we have called typical. Bases and Kurtin [27] maintain that bronchoscopy may be life saving in cases of asthma.

The blood pressure in asthma fluctuates during the phases of respiration. This has been described, but Osgood has investigated the matter in a special study. In 1942 [28] he obstructed the tracheas of cats and the mouths of human volunteers. He found that as the respiratory effort increased, the systolic blood pressure fell during inspiration. This year [29] he has studied patients with asthma and found that fluctuations of the systolic blood pressure are a constant finding. The high point occurs during expiration and the low point during inspiration, and the amplitude of the difference is closely parallel to the severity of the asthma. I can add to this that the fluctuation does not occur in all cases and is distinctly greater in older persons who have emphysema than it is in younger patients. I believe that the sign may be of diagnostic importance, but unfortunately the study has not gone far enough to indicate the cause of the drop except to show that it depends on the sucking effect, the increased negative pressure of active inspiration. Whether this affects the output of the right or of the left ventricle more or affects both at the same time and equally is hard to say.

Somewhat related are the observations of Vaccarezza and Cucchiani Acevedo,[30] from Buenos Aires. In 3 cases of pulmonary tuberculosis associated with asthma they made direct measurements of the intrapleural pressure before, during and after acute paroxysms of asthma. They found that during the attack of asthma there was a definite increase of intrapleural pressure, and in 2 cases in which pneumothorax had been induced they removed some of the air and brought relief from the symptoms. After the attack had been relieved by epinephrine, the collapse of the lungs was even greater than before.

The Heart.—The heart in asthma is always interesting, partly because the nature of so-called "cardiac asthma" is so obscure and partly because in every case of severe asthma the doctor fears that the heart may give away.

Schiller, Colmes and Davis [31] made special studies of the heart in 69 cases. In 15 of these the patients died and autopsy was performed. In 3 the asthma had lasted for less than three years, and the heart was normal. In 12 the asthma had lasted for over six years, and in 4 of these there were right-sided heart strain and death in failure (cor pulmonale). Of 54 living patients, however, only 1 had any clinical evidence of heart failure. The electrocardiograms, on the other hand, revealed a number of abnormalities: There was deviation of the axis to the right in 18 per cent of the patients whose asthma had lasted for more than ten years. The authors state that cor pulmonale is more common than is usually believed. If a careful study reveals trouble in less than a quarter of the cases it would seem that on the whole the heart keeps going on well in spite of its increased burden. The method by which Sussman, Steinberg and Grishman [32] could inject a radiopaque substance into the blood stream and then under the fluoroscope study the action of the different chambers of the heart in various diseases, notably in emphysema, is illuminating. Their article contains a series of handsome photographs and diagrams.

26. Friedberg, S. A.: Bronchoscopy and Asthmatoid Respiration, J. A. M. A. **123**:85 (Sept. 11) 1943.

27. Bases, L., and Kurtin, A.: Prevention of Death in Status Asthmaticus: Value of Bronchoscopy, Arch. Otolaryng. **36**:79 (July) 1942.

28. Osgood, H.: Blood Pressure Fluctuations in Respiratory Obstruction, J. Lab. & Clin. Med. **27**:1536, 1942.

29. Osgood, H.: Blood Pressure Fluctuations in Bronchial Asthma, J. Lab. & Clin. Med. **28**:927, 1943.

30. Vaccarezza, R. F., and Cucchiani Acevedo, R.: Artificial Pneumothorax in Pulmonary Tuberculosis Complicating Asthma, An. Cáted. de pat. y clín. tuberc. **3**:67, 1941.

31. Schiller, W.; Colmes, A., and Davis, D.: The Occurrence of Cor Pulmonale in Cases of Bronchial Asthma, New England J. Med. **228**:113, 1943.

32. Sussman, M. L.; Steinberg, M. F., and Grishman, A.: Contrast Visualization of Heart and Great Vessels in Emphysema, Am. J. Roentgenol. **47**:368, 1942.

Periarteritis Nodosa.—In July 1942 Rich,[33] of Baltimore, submitted an important paper in which he gives evidence that periarteritis nodosa is a part of serum disease. Rich points out that, whereas deaths from serum disease are extremely rare, the use of sulfonamide drugs has prolonged life so as to permit serum disease to develop before death. He collected 6 cases in which the patients died during serum disease and another case in which a biopsy of muscle taken during serum disease showed similar lesions. In addition, Rich recalls that Clark and Kaplan[34] in 1937 had found 2 patients who had died during serum disease. In 2 cases of Clark and Kaplan and in the seventh case in his own series there had been no treatment with sulfonamide drugs. In each of these 9 cases autopsy showed the familiar lesions of periarteritis nodosa, necrosis of the walls of the blood vessels and fibrinoid alteration, with hyalinization later, all associated with local hemorrhages as well as with local eosinophilia. Were these lesions due to the disease, to the serum or to the drug? The fact that 3 patients had not received any sulfonamide drug rules out the last possibility, and, furthermore, in 1 case a maculopapular rash, different from the urticaria, had appeared with the beginning of treatment with the drug and subsided when it was discontinued and before the urticaria had appeared. The vascular lesions were fresh. As for the disease factor, the very fact that periarteritis nodosa should have occurred in several different diseases when it was not a part of the ordinary pathologic process of those diseases makes it almost sure that its development depended on the serum.

In a second paper, submitted in November 1942, Rich and Gregory[35] describe how the lesions of periarteritis nodosa could be reproduced in rabbits. Fourteen animals received horse serum in doses of 10 cc. per kilogram of body weight, and 5 of them received sulfadiazine in addition. Most of the rabbits acquired the flush which Fleischer and Jones[36] had described as the counterpart of serum disease in rabbits. On the twelfth day skin tests showed all the rabbits to be sensitized, and on the seventeenth day all were reinoculated, with 1 cc. of horse serum. However, only 2 of the animals died. After that, some of the animals were killed and others were reinoculated with horse serum in different amounts at different intervals. When these animals were killed and autopsies were performed, every state of periarteritis nodosa could be demonstrated in the blood vessels: The endothelium was damaged, fluid and inflammatory cells appeared in the adventitia and the muscle became hyalinized and necrotic later.

It is important that Rich and Gregory could produce these lesions in rabbits by treatment with horse serum alone. Indeed they showed that the lesions could result from a single large injection of horse serum. Sulfadiazine did not play any direct part in producing the typical pathologic pictures.

Baker[37] reports 2 cases of periarteritis nodosa, and gives an extensive description of the clinical, laboratory and pathologic observations. The first case was that of a man aged 39 who had had severe asthma for two years. About a year before his death pain and swelling suddenly developed in the legs, and later came other swellings and purpuric spots. The first blood counts showed only 5 to 8 per cent of eosinophils, but toward the end his white cell count rose to 25,000 and the eosinophils to 70 per cent. At autopsy the vessels in all the organs showed periarterial infiltration with fibrosis. The second patient was a man aged 47 admitted to the hospital because of fever, weakness and bodily pains of about one week's duration. He lived for five months and during that time had a progressively downhill course. Peripheral neuritis developed, and also a progressive retinitis. Petechial hemorrhages appeared at the end, and he died of heart failure. At no time did he have any asthma or any other symptoms of allergy. His white cell count rose only to 15,000, and the proportion of eosinophils was never above 2 per cent. Autopsy was refused, but a biopsy of the gastrocnemius muscle showed extensive periarterial lesions with fibrous proliferation, numbers of lymphocytes and scattered eosinophils. In the media of the larger arterioles were collections of pale cells forming pseudotubercles. (Giant cells have been described by other pathologists.) These cases are summarized here in order to emphasize that, whereas periarteritis nodosa occurs in patients

33. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123, 1942.

34. Clark, E., and Kaplan, B. I.: Endocardial, Arterial and Other Mesenchymal Alterations Associated with Serum Disease in Man, Arch. Path. **24**:458 (Oct.) 1937.

35. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65, 1943.

36. Fleischer, M. S., and Jones, L. R.: Serum Sickness in Rabbits: I. Manifestations of Serum Sickness, J. Exper. Med. **54**:597, 1931.

37. Baker, L. A.: Periarteritis Nodosa, with Report of Two Cases, Ann. Int. Med. **17**:223, 1942.

with severe asthma, it may occur also in other conditions.

Important is a recent paper by Selye and Pentz,[38a] who have carried the study much further. They point out that the lesions of periarteritis nodosa are similar histologically to the arterial lesions in the kidneys of patients with malignant hypertension and are reminiscent of rheumatic foci. (Rheumatic fever and periarteritis nodosa occur together with some frequency.) They also point out that the lesions of periarteritis nodosa have been produced by treatment with a number of different substances, by injections of various proteins, by injection of streptococci and by feeding a high protein diet to unilaterally nephrectomized rats. "Nephrotoxic" serums are often described. Selye and Pentz found that certain steroid hormones were potent in producing nephrosclerosis and that at the same time extrarenal vessels were often damaged by these hormones. Rats were given extra salt in their diet, and then some of the animals had one kidney removed. When the animals were treated with desoxycorticosterone acetate the lesions were produced (more in the group operated on), and the photographs which accompany the paper show the typical changes of periarteritis nodosa. The authors explain that a sudden stress, such as cold, fatigue or infection, may elicit the "alarm reaction," and "if the damaging stimulus continues, it is followed by the resistant stage and eventually by the exhaustion stage of the general adaptation syndrome. . . . It has been found that exposure to cold or other damaging agents causes rats sensitized by salt treatment, unilateral nephrectomy or preferably both to have pathologic changes identical with those produced by administration of desoxycorticosterone acetate."[38b] During this process the adrenal cortex increases in size and produces excessive amounts of its hormone. Meantime, body proteins break down or perhaps foreign proteins are injected, and lesions result. The fact that acute infections, nervous shock, exposure to cold (and, I can add, repeated attacks of asthma) are sometimes followed by periarteritis nodosa or nephrosclerosis or rheumatic fever indicates that these conditions are diseases of adaptation dependent on an abnormal adaptive response of the adrenal cortex. It is an interesting conception, and it is based on what appears to be good experimental observation and evidence.

From all this it is clear that periarteritis nodosa is not a disease—it is only a lesion which develops from a variety of causes and in a number of different diseases. Furthermore, it does not point to any particular specific exciting factor.

Treatment of Asthma.—Since 1934 Barach[39] has been recommending the use of helium-oxygen mixtures administered by inhalation to relieve the severe paroxysms of asthma. He has now developed a plan of "bronchial relaxation," as he calls it, which in his hands at least is successful. When the patient is first admitted to the hospital, theophylline ethylenediamine is given by rectum at once—0.5 Gm. in 20 cc. of water. A strong (1 : 100) solution of epinephrine hydrochloride is used as a spray to be inhaled through the nose and/or mouth from a special atomizer connected with an oxygen tank. Dihydromorphinone hydrochloride in doses of 1 or 2 mg. is given subcutaneously if necessary. Finally a gas mixture containing 20 per cent oxygen and 80 per cent helium is administered by inhalation through a special apparatus. The first dose of potassium iodide (1 cc. of the saturated solution in water) is also given early. The inhalation of the helium-oxygen mixture is continued for two hours in the average case, but it may be continued for twelve hours or given intermittently, according to the need. When the patient improves and becomes ambulatory, he reports to the clinic for treatment, and if he still has asthma theophylline ethylenediamine is again given by rectum, the epinephrine spray is repeated and he inhales the helium-oxygen mixture, 7 to 9 liters per minute, for about an hour. This treatment produces "bronchial relaxation" and is repeated every day for five days as indicated.

The immediate results of this treatment are good. In the hospital there were 26 patients who received 46 courses of treatment. After 34 of the courses the asthma disappeared, and only three courses were ineffective. There were 45 ambulatory patients who received 54 courses of treatment. The asthma disappeared after 23 of these courses, and only 14 were ineffective. The long term results were likewise good. Relief lasted from one to four weeks in 36 of 57 patients who were followed. It lasted from one to four months in 20 patients, from five to twelve months in 20 and for over a year in 15. Segel[40]

38. (*a*) Selye, H., and Pentz, E. I.: Pathogenetical Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, Canad. M. A. J. **49**:264, 1943. (*b*) Selye, H.: Unpublished communication.

39. Barach, A. L.: Repeated Bronchial Relaxation in the Treatment of Intractable Asthma, J. Allergy **14**:296, 1943.

40. Segel, M. S.: Inhalational Therapy in the Treatment of Serious Respiratory Disease, New England J. Med. **229**:235, 1943.

has tried the method on 4 patients; 1 died, but the other 3 did well.

Westcott and Gillson [41] did not use Barach's method in full, but at least they agree that inhalation of a strong (1:100) solution of epinephrine hydrochloride does good. Their paper, however, lays stress on the importance of breathing exercises, which they say can produce a substantial increase in the vital capacity and which will ultimately lead to a considerable relief of the asthma.

More recently Lockey [42] has tried to overcome the disadvantages of the strong (1:100) epinephrine hydrochloride solution spray, which he says tends to dry the throat and to produce palpitations and "jitters" in certain patients. He adds glycerin, hydrochloric acid, sodium chloride, chlorobutanol and sodium bisulfite to the epinephrine hydrochloride solution and claims that his prescription is less irritating.

Literature on drug treatment includes a number of new suggestions. The status of theophylline ethylenediamine and of related xanthine derivatives has been reviewed by Boyer.[43] Ethylenediamine is added to theophylline because the double salt is more soluble. The effect, however, depends on the xanthine compound. This is a diuretic; it increases the contraction of the heart muscle, and it can relieve Cheyne-Stokes breathing. Macht and Ting [44] showed that theobromine dilates the excised bronchi. Young and Gilbert [45] found that it has a protective effect against histamine. Whatever the mechanism, theophylline ethylenediamine is clinically useful in asthma. Dees [46] has found that suppositories of this compound are good.

Maietta [47] found that doses given intramuscularly at intervals of four to six hours were helpful to patients with severe status asthmaticus. Paraldehyde is a powerful sedative, the effect of which is often immediate, so that after receiving a dose of 1 or 2 cc. by mouth the patient relaxes within five minutes. Burstein [48] warns that there is danger in giving too much paraldehyde. The injection of as much as 30 cc. by rectum caused the death of a young woman. Another patient received 15 cc. in two doses six hours apart with no effect but three hours after the third dose she died. These amounts, however, are much too large. In the ordinary case, 1 or 2 teaspoons of paraldehyde (4 to 8 cc.) given by mouth is sufficient to produce a dopey sleep, and in any one night 2 teaspoons are all that is required in most cases.

Ether in oil is now available in ampules containing 1 cc. of ether with 1 cc. of peanut oil.

Nicotinic acid has been suggested for use in treatment. Suranyi [49] gave it to allergic children in doses of 25 or 50 mg. twice a day. The effect of nicotinic acid is somewhat similar to the effect of histamine, and doses given by mouth are often followed by the appearance of erythema and a feeling of heat and warmth. Urticaria, asthma and spastic bronchitis were found to respond favorably. The drug is said to be useful for certain types of headache, as will be discussed. Nicotinic acid is a vasodilator drug.

Nucleic acid is used by Howe [50] in the treatment of subacute and chronic sinusitis with the idea that the condition depends either on a deficiency of nucleoproteins in the diet or on faulty absorption of these substances. So far, however, there is not much evidence to support either of these theories. Potassium salts have been advised for some years. Carlson and Whitehead [51] review the literature. They found that the feeding of sodium salts to guinea pigs suffering from anaphylactic shock had no protective effect but that potassium salts could save the animals from death.

Sulfonamide drugs have been advocated for the treatment of asthma, as might be expected. Jiménez-Díaz and his co-workers [52] gave sulfa-

41. Westcott, F. H., and Gillson, R. E.: The Treatment of Bronchial Asthma by Inhalation Therapy with Vital Capacity Studies, J. Allergy **14**:420, 1943.

42. Lockey, S. D.: Inhalation of Oxygen and 1:100 Epinephrine Hydrochloride Plus Five per Cent Glycerin for the Relief of Asthmatic Attacks, J. Allergy **14**:382, 1943.

43. Boyer, N. H.: Aminophylline and Related Xanthine Derivatives: Present Status of Therapeutic Claims, J. A. M. A. **122**:306 (May 29) 1943.

44. Macht, D. J., and Ting, G.-C.: A Study of Antispasmodic Drugs on the Bronchus, J. Pharmacol. & Exper. Therap. **18**:373, 1921.

45. Young, R. H., and Gilbert, R. P.: The Use of Theophylline with Ethylenediamine (Aminophyllin) for the Control of Bronchial Spasm, J. Allergy **12**:235, 1941.

46. Dees, S. C.: The Use of Aminophylline Rectal Suppositories in the Treatment of Bronchial Asthma: Preliminary Report, J. Allergy **14**:492, 1943.

47. Maietta, A. L.: The Use of Ether in Oil Intramuscularly in the Treatment of Bronchial Asthma, New England J. Med. **227**:985, 1942.

48. Burstein, C. L.: The Hazard of Paraldehyde Administration: Clinical and Laboratory Studies, J. A. M. A. **121**:187 (Jan. 16) 1943.

49. Suranyi, J.: Suggestion for Treatment of Allergic Conditions, Ann. pædiat. **158**:231, 1942.

50. Howe, A. C.: Nucleic Acid Treatment of Subacute and Chronic Sinusitis, Ann. Otol., Rhin. & Laryng. **51**:220, 1942.

51. Carlson, R. G., and Whitehead, R. W.: The Effect of Sodium, Potassium, and Thiosulfate Ions on Anaphylaxis, J. Allergy **14**:462, 1943.

52. Jiménez-Díaz, C.; Lahoz, C., and Recatero, L.: Sulfapyridine Therapy of Persistent Bacterial Asthmas, Rev. clín. espãn. **4**:423, 1942.

pyridine to 10 patients with status asthmaticus, and in 8 of them the therapy effected a disappearance of all symptoms. The authors' explanation is that bacterial infection played an important part. My associates and I have tried sulfonamide compounds in a few cases, but our results have not been good, and there is always the danger of producing another specific sensitiveness to complicate the picture.

Last winter the laity read about a new treatment for asthma described in the daily press. Some editor was intrigued by Lapp's [53] claim that small doses of the patient's own serum can be given at regular intervals to produce a "desensitization" and cure his asthma. The idea is not new. It developed originally from the conception that the causative antigen is absorbed into the blood stream and that the blood can be assumed to contain it even though its nature is unidentified. Originally the method was to defibrinate the blood and then reinject a relatively large quantity, perhaps 20 to 50 cc., into the muscle. A simpler method is to draw blood from a vein of the arm and then, while it is still "hot" and uncoagulated, to inject it immediately, with the same needle and syringe, into the buttock. The procedure is somewhat dramatic, and it is a little painful. More important, it carries the considerable danger that the pool of blood that is produced at the site of the injection may become infected. I doubt if the method has much more than a psychologic value, but in some cases this appears to be considerable.

There are several new methods for making the absorption of injected drugs slow and prolonged. Abramson and Arsenal [54] add gelatin to epinephrine. Spain and his co-workers [55] recommend gelatin as a vehicle for ragweed pollen extract. In order to reduce the power of jelling and to make the material less viscid, they treated the gelatin solution in the autoclave at 20 pounds' (9 Kg.) pressure for one and three-quarters hours. The gelatin hydrolyzed and as such was added to the strong pollen extract to make the gelatin-pollen mixture. With this material 28 of 55 patients had little or no hay fever, whereas with the ordinary watery pollen extract only 14 of 55 patients had really good results. Naterman [56] uses epinephrine base suspended in an aqueous solution of sodium thioglycolate, which is an acid-reducing agent and so prevents the epinephrine base from being oxidized too rapidly.

Suspensions of epinephrine base in oil have been studied by Richards.[57] In experiments on rats he found that the toxicity of the preparations was the same as that of aqueous solutions of epinephrine hydrochloride. Furthermore, experiments designed to demonstrate a more prolonged action of the oil mixture by means of blood sugar curves did not give any impressive result. When the size of the particles was reduced by special grinding, the toxicity was less, possibly because the small particles were better protected by a film of oil, which delayed their absorption.

Oil has been used to delay the absorption of pollen. Taub and Rubens [58] made a 3 per cent extract of pollen in water and then evaporated it to dryness under vacuum. This lyophilized pollen was then homogenized electrically into sterile sesame oil. When this material was used for skin tests the positive reaction was delayed for about thirty minutes in its appearance.

Meantime, Foldes [59] has worked with a different principle in trying to prolong the action of subcutaneously injected medicaments. He recalled that certain metals can prolong the action of injected drugs, and so he used zinc chloride in concentrations of 0.1 per cent or less. With posterior pituitary extract, the antidiuretic action is much prolonged. When zinc chloride was added to epinephrine hydrochloride solution, the mobilization of blood sugar was delayed to a definite degree. In another experiment he tried his "zinc-epinephrine" solution on a patient with asthma. There was no delay in the onset of the antiasthmatic effect, but he observed that the effect lasted for six to eight hours instead of the usual three to four hours. The plan deserves further study.

Finally, a paragraph from a recent paper by Sir Arthur Hurst [60] is copied in full. "Every

53. Lapp, A. D.: Asthma Treated with Patient's Blood Serum, Brit. M. J. **1**:552, 1942.

54. Abramson, H. A., and Arsenal, E.: A U.S.P. Gelatin Vehicle in Liquid Form for Retardation of Absorption with Special Reference to Epinephrine, J. Allergy **14**:414, 1943.

55. Spain, W. C.; Fuchs, A. M., and Strauss, M. B.: The Treatment of Hay Fever with Gelatin-Pollen Extracts, J. Allergy **14**:376, 1943.

56. Naterman, H. L.: Adrenalin Base Suspended in an Aqueous Solution of Sodium Thioglycolate in the Treatment of Asthma, New England J. Med. **227**:736, 1942.

57. Richards, R. K.: A Pharmacologic Study of Epinephrine Suspensions in Oil, J. Allergy **14**:177, 1943.

58. Taub, S. J., and Rubens, E.: Pollen Oil: A Preliminary Report on a New, Slowly Absorbed Medium for the Use in Hay Fever Treatment, Ann. Int. Med. **17**:642, 1942.

59. Foldes, F. F.: The Prolongation of the Action of Subcutaneously Injected Medicines in Man, J. Clin. Investigation **22**:499, 1943.

60. Hurst, A.: Asthma in Childhood, Brit. M. J. **1**:403, 1943.

asthmatic can derive much benefit from good advice. He can be taught a way of life; how to avoid the exciting causes of his particular brand of asthma, how to control attacks he is unable to prevent, and above all, how to be happy in spite of the bad luck of having been born with the asthma diathesis."

Results of treatment are not often described. Unger and Wolf [61] describe the status of 207 patients followed for seven years or more after the first treatment. Those who were free of symptoms continued well, and of 104 previously reported as improved, 19 were free of asthma. Another 252 patients have been added to the study, to make a total of 459. Of these, 298, or 65 per cent, had "paroxysmal asthma" and 93 were well, whereas only 4 of 161 patients with chronic persistent asthma were free of symptoms. Best results were obtained in patients whose paroxysmal asthma was caused by some allergen which could be found and eliminated. These are the persons who began to have asthma early in life. Forty-eight patients had died; the asthma was the main cause of death of 21, and the contributing cause for 16. Morphine was known to have been given just prior to death to 6 patients. Presumably these were patients whose asthma began late in life (after the age of 45) and who therefore had quite a different disease from those whose asthma began before the age of 30. In any study of end results in asthma the clincial classification of the patient is of primary importance.

Describing the results of operations on the sinuses in cases of chronic infection, after an interval of two to eight years, Cooke [62] reports that of 74 patients operated on 52 per cent have had little or no asthma and only 8 are not improved, but of 78 patients that were not operated on only 13 per cent have been relieved and 64 are not improved. Needless to say, he lays stress on the selection of cases and on the technic of operating. (Such results cannot be obtained in my clinic.)

CHEMICAL EFFECTORS

The mechanism by which asthma and the other manifestations of hypersensitiveness are produced is not at all clear, but the study of the problem still centers around the chemical effectors—the powerful substances which are normally present in the body and which are released by various exciting factors. Nerve impulses exert their effect through the effectors, especially acetylcholine, whereas direct stimulation, as by injury or perhaps by antigen-antibody reactions on the surface of cells, causes the release of histamine from those cells.

When antigen is mixed with sensitive blood in vitro, histamine is released from the cells and can be found in the plasma. Dragstedt, Wells and Rocha e Silva [63] found that when heparin was added to the blood to prevent clotting the quantity of histamine released was less than without heparin. Furthermore, this inhibition was about the same whether sensitive blood was treated with antigen or whether normal blood was treated with trypsin or peptone. This is further evidence that the mechanism of peptone shock is not different from that of anaphylactic shock. In another experiment, Dragstedt [64] treated a large number of dogs with peptone, 10 per cent Bacto-protone (Difco) in doses of 2 cc. per kilogram. The primary injection often caused severe reactions, but in some of the dogs it was possible to raise the resistance to subsequent doses. Refractoriness to peptone cannot, however, be effected without inducing shock, and the degree of resistance is determined usually by the severity of that shock. Dragstedt found a good deal of crossed relationship between shock of different kinds. Animals made refractory to Witte's peptone, derived from fibrin, were refractory to Armour's peptone, made from milk. The relation between peptone shock and anaphylactic shock was fairly close. When mild anaphylactic shock was induced in sensitized dogs, a subsequent dose of peptone caused a severe reaction in over half the animals. When, however, the anaphylactic shock was more severe, only 3 of the 13 animals reacted severely to the subsequent dose of peptone. Refractoriness to peptone has nothing to do with the binding of antigen to antibody; it is concerned chiefly with the reaction itself, that is, with the release of the chemical effector. Essex and Horton [65] were able to increase the resistance of guinea pigs to histamine to some extent by treating their animals with histamine in small subcutaneous doses. Of the pretreated animals,

61. Unger, L., and Wolf, A. A.: Treatment of Bronchial Asthma: A Survey of the Value of Treatment in Four Hundred and Fifty-Nine Cases During Twenty Years, J. A. M. A. **121**:325 (Jan. 30) 1943.

62. Cooke, R. A.: The Practitioner and the Allergy Problem, with Special Reference to Respiratory Allergy, Rhode Island M. J. **25**:152, 1942.

63. Dragstedt, C. A.; Wells, J. A., and Rocha e Silva, M.: Inhibitory Effect of Heparin upon Histamine Release by Trypsin, Antigen and Proteose, Proc. Soc. Exper. Biol. & Med. **51**:191, 1942.

64. Dragstedt, C. A.: Observations on Spontaneous and Induced Refractoriness to Peptone Shock in Dogs, J. Immunol. **47**:1, 1943.

65. Essex, H. E., and Horton, B. T.: Observations on Development of Resistance to Histamine in the Guinea Pig, Proc. Staff Meet., Mayo Clin. **16**:603, 1941.

27, or 41 per cent, survived the lethal dose, as compared with only 5 per cent of the controls.

Thyroid depletes the stores of ascorbic acid and cholesterol in the adrenal glands. According to Farmer and Fribourg [66] this results in a depletion of the cortical hormone, and this in turn produces an increase in sensitiveness to histamine. Animals fed thyroid for several days were more susceptible to histamine than were the untreated controls.

Wilcox and Seegal [67] found an ethylenediamine derivative which would protect guinea pigs against 1 to 6 minimal lethal doses of histamine although cyanosis and prostration without death occurred in many animals. They believed that the drug acted primarily to prevent contraction of the smooth muscle but not to prevent the development of other manifestations of shock. Courtright, Hurwitz and Courtright [68] produced anaphylactic shock by exposing guinea pigs sensitive to horse dander to inhalation of the specific dust, and he tried to protect them by treatment with histamine and with acetylcholine as well as with histaminase. Even though the doses and intervals were varied considerably, he was unable to demonstrate any definite preventive action by any one of the three substances.

Histamine in the treatment of clinical allergy has been recommended. Farmer and Kaufman [69] gave histamine subcutaneously, increasing the doses at frequent intervals, for the treatment of chronic vasomotor rhinitis as well as of hay fever. In 41 cases of perennial rhinitis, the results were good in 25 instances, fair in 10 and poor in 6. In 24 cases of severe ragweed hay fever, the results were good in 7 and fair in 9. In 48 cases of moderate ragweed hay fever, the results were good in 19 and fair in 13, and in 15 cases of grass hay fever, the results were good in 9 and fair in 6. The result of treatment was better in the cases of perennial rhinitis. More recently, Gant, Savignac and Hochwald [70] have given histamine by mouth, for treatment of chronic vasomotor rhinitis. They find that the drug is absorbed rapidly from the gastrointestinal tract and that when the patient starts with a small dose, perhaps with 1 drop of a 1:10,000 dilution of histamine in water, and then increases the amount by slow, careful increments, a dose is soon found which causes a sense of warmth and flushing of the skin, and when this occurs the nasal symptoms improve. The size of that dose is noted carefully, and thereafter the same quantity is taken two or three times a day, as often as may be necessary to secure relief. The trick is to find the dose, which may vary in different cases from 1 drop of a 1:10,000 dilution (0.01 mg.) to 5 drops of a 1:100 dilution (3 mg.). Enough patients have been relieved by this method to justify further study of it.

Histamine in the treatment of Ménière's syndrome has been recommended for some years. Rainey [71] reports on 6 patients who were treated with histamine phosphate intravenously. The ampule containing 2.75 mg. in 1 cc. is diluted to 250 cc. with isotonic solution of sodium chloride to make a 1:100,000 dilution of histamine phosphate. The speed of injection is important, for in some cases as much as 20 drops a minute will cause flushing and headache, while in others 70 drops a minute is borne without difficulty. After the initial intravenous treatment, further doses may be given at intervals subcutaneously. All 6 of Rainey's patients did well.

Atkinson [72] also uses histamine for Ménière's disease, but he has found it important to distinguish the patients whose headaches depend on vasoconstriction and whose skins are not sensitive to histamine from the other group, whose headaches depend on vasodilatation and who show an extensive reaction to histamine in a skin test. Atkinson assumes that histamine is in part responsible for the normal balance of vasodilatation against vasoconstriction. Added histamine will have an immediate vasodilator action, and the headache will be relieved, but meantime it will tend to produce an increased resistance of the body toward histamine, so that vasoconstriction will be favored. When the headache is due to

66. Farmer, L., and Fribourg, R.: Studies on Histamine Sensitivity and Anaphylactic Response: The Effect of Thyroid Extract, Proc. Soc. Exper. Biol. & Med. **50**:208, 1942.

67. Wilcox, H. B., Jr., and Seegal, B. C.: Influence of an Ethylendiamine Derivative on Histamine Intoxication and Anaphylactic Shock in the Intact Guinea Pig and Isolated Guinea Pig Heart, J. Immunol. **44**:219, 1942.

68. Courtright, L. J.; Hurwitz, S. H., and Courtright, A. B.: Inhalant Sensitization and Shock in Guinea Pigs Under Controlled Atmospheric Conditions: II. Histamine, Histaminase, and Acetylcholine as Possible Preventives, J. Allergy **13**:444, 1942.

69. Farmer, L., and Kaufman, R. E.: Histamine in the Treatment of Nasal Allergy (Perennial and Seasonal Allergic Rhinitis), Laryngoscope **52**:255, 1942.

70. Gant, J.; Savignac, R. J., and Hochwald, A.: Histamine by Mouth in the Treatment of Vasomotor Rhinitis, New England J. Med. **229**:579, 1943.

71. Rainey, J. J.: Histamine in the Treatment of Ménière's Syndrome, J. A. M. A. **122**:850 (July 24) 1943.

72. Atkinson, M.: Histamine in the Treatment of Ménière's Syndrome, J. A. M. A. **119**:4 (May 2) 1942.

vasodilatation, this is desirable, but headaches due to vasoconstriction will be made worse. For these nicotinic acid, given in doses of 50 mg. by vein at first and by mouth later, appears to be effective.

Neostigmine for treatment of headache is suggested by Pelner.[73] If acetylcholine is the effector which causes trouble, neostigmine, by blocking the cholinesterase, should prevent the destruction of acetylcholine and allow its absorption. Pelner found that prostigmine bromide given in doses of 15 mg. by mouth produced a headache, and so he dissolved the tablet in an ounce of tap water and then prescribed drop doses of the solution by mouth. Like Atkinson, Pelner considered the finding of a positive reaction to a skin test with histamine 1:1,000 and with acetylcholine 1:20 as the necessary criterion for success. Of 46 patients, 37 were completely relieved and 5 were much improved by Pelner's treatment.

Atropine prevents the action of acetylcholine, and it is interesting to have Bender, working in Abramson's laboratory,[74] find that atropine could inhibit the cutaneous reactions caused by mecholyl but not the flare caused by histamine (the reactions being produced by driving the substances through the skin with an electric current).

ANAPHYLAXIS

Death following the injection of foreign protein is still reported, in spite of increasing knowledge of the dangers. Vance and Strassmann[75] collected from the records of the chief medical examiner of the city of New York the accounts of 7 necropsies. Five were of persons who died suddenly after an injection of antitoxin, and 2 were of allergic persons who were killed by specific treatment. One of these was a child who died shortly after an intracutaneous test with a mixture of silk, wool and kapok extracts. The other was an asthmatic adult who died after a routine injection of ragweed extract. In each case the lungs were greatly distended (insufflated) and the viscera were congested. From the literature the authors collected the reports of 18 similar cases. Of the total of 25 patients, all except 3 patients died within ten minutes after the injection, and the 3 died in six hours, fourteen hours and twenty-three hours respectively. Of the total 25, only 13 had a history of any previous treatment with foreign proteins, and the authors postulate a hereditary constitutional factor in addition to anaphylaxis.

About a year ago two groups of patients in a hospital for persons with mental disease were given small doses of guinea pig serum in order to study the development of hypersensitiveness. One of them, an apparently healthy woman of 22, died within ten minutes after receiving 0.2 cc. of guinea pig hemoglobin injected intradermally. At autopsy, an acute hemorrhagic inflammatory reaction was found at the site of treatment; there were edema of the upper air passages and emphysema with large pleural bullae. The case was studied by the medical examiner, Dr. Hunt.[76] The first question was whether the woman was actually sensitive, and an interesting experiment was made. Her serum obtained from the heart's blood was found to sensitize the skin of 3 normal recipients so that the prepared sites reacted well to solutions of guinea pig hemoglobin. The diagnosis of allergy and anaphylaxis was proved. In passing, let me observe that reagins were still demonstrable in spite of and immediately after the overwhelming reaction.

A comment on this case appeared subsequently in *The Journal of the American Medical Association*[77] and included the following statement: "Close inquiry disclosed that the mother of the subject of this report had asthmatic attacks and symptoms of hay fever, that a brother suffered from hay fever and that the mother's first cousin, also asthmatic, died at the age of 16, ten minutes after the subcutaneous injection of diphtheria antitoxin, the first death of that kind in this country. The lesson again brought home by the bare facts in Dr. Hunt's report is that the most watchful precaution must always be taken to avoid fatal shock on the injection of foreign protein antigenic material into human beings."

INDUSTRIAL DERMATITIS

Industrial dermatitis appears to be a fairly constant menace, even though the total number of cases is not large. A report of the Committee on Occupational Dermatoses of the American Medical Association, presented by Foerster and

73. Pelner, L.: The Treatment of Periodic Occipital Headache with "Desensitizing" Doses of Prostigmine, Dis. Nerv. System **4**:177, 1943.

74. Bender, M. B.; Abramson, H. A., and Ehrlich, G.: Skin Reactions: XIV. The Effect of Atropine on the Mecholyl and Whealing Reactions of the Skin, J. Mt. Sinai Hosp. **9**:322, 1942.

75. Vance, B. M., and Strassmann, G.: Sudden Death Following Injection of Foreign Protein, Arch. Path. **34**:849 (Nov.) 1942.

76. Hunt, E. L.: Death from Allergic Shock, New England J. Med. **228**:502, 1943.

77. Kortright, J. L.: Practical Experiences with Antitoxin, Brooklyn M. J. **10**:87, 1896.

others,[78] describes in some detail the methods of diagnosis, prevention and treatment. The allergic background of each employee should be studied, and attention should be paid to any neurogenic or psychogenic relationships. Habits of eating and living may need a good deal of correction.

Oil folliculitis and dermatitis are not uncommon. Cutting oils may be of animal, vegetable or mineral composition, and the prevention of the dermatitis which may follow their use is chiefly a matter of personal cleanliness, the achievement of which can be facilitated by adequate provision for washing hands, body and clothes. Sulfonated oils are produced by treating natural oils with sulfuric acid and then neutralizing the excess acid with an alkali. Some of these preparations mix well with water to form creamy emulsions and become useful as cleansing agents. The new development of "soapless soap" depends primarily on the use of sulfonated oils of one sort or another. Occasionally, however, trouble may come from these preparations.

Zinc dermatitis is described by Freeman[79] as a hazard in the aircraft industries, where certain alloys are used. Patch tests with zinc elicit positive reactions in the victim and quite negative reactions in controls. Sodium chromate and sodium dichromate are encountered in the production of air-conditioning equipment. Schwartz and Dunn[80] found that 14 per cent of 105 workers had dermatitis which could be attributed to that cause. Sodium dichromate is also used as a wetting agent for the dyes employed in the manufacture of blankets for the Army, and the same authors[81] found trouble in this group of workers also. Dermatitis due to resin finishes for cotton fabrics, especially underwear, has been described by Keil[82] and also by Costello and Ryan,[83] the latter reporting on 20 cases which were observed at the Bellevue Hospital in New York.

Dhobie is a nut tree in India. Its sap turns black and so makes a convenient fluid for marking clothes. Goldsmith[84] found that the soldiers developed a dermatitis under the neck band or at the waist where the marks touched the skin. It was difficult to get rid of the sensitizing effect of the marks. Boiling of the clothes was ineffective. Dermatitis of the face from contact with the rubber parts of gas masks is described by Petro,[85] who demonstrated positive reactions to patch tests with the "accelerator" and the "antioxidant" used in the manufacture of that particular rubber. Fox[86] describes a farmer who became sensitive to the dust of mesquite wood. Patch tests with the ether extract of the sawdust produced a positive reaction. Contact dermatitis from cod liver oil is described by Cope.[87]

Cosmetics still hold an important place in the list of causes of contact dermatitis. Simon[88] observed 13 patients with eczema of the face who gave positive reactions to patch tests with five different brands of nail lacquer, both colorless and colored. After avoidance of the lacquer 11 of the 13 patients were cured at once. Patch tests made with a variety of different ingredients showed reactions to a certain formaldehyde-sulfonamide resin which was used in making the lacquer. More recent are reports by Howell[89] and by Epstein[90] describing contact dermatitis from hair lacquer, a new preparation and evidently an important feature of the latest "up-do" coiffure.

As has been said elsewhere, it is evident that the list of substances capable of producing local reactions on the human skin is never complete, especially in this modern day when chemicals, both old and new, are being used more and more even in what appear to be fairly simple and clean processes.

78. Foerster, H. R., and others: Recognition and Prevention of Industrial Dermatitis, with Additional Reference to Oil Dermatitis and Folliculitis: A Report of the Committee on Occupational Dermatoses, American Medical Association, J. A. M. A. **122**:370 (June 5) 1943.

79. Freeman, H. E.: Zinc Dermatitis: An Additional Hazard in Aircraft Industries, J. A. M. A. **119**:1016 (July 25) 1942.

80. Schwartz, L., and Dunn, J. E.: Dermatitis Occurring Among Operators of Air-Conditioning Equipment, Indust. Med. **11**:375, 1942.

81. Schwartz, L., and Dunn, J. E.: Dermatitis Occurring in a Woolen Mill, Indust. Med. **11**:432, 1942.

82. Keil, H.: Dermatitis Due to Resin-Finished Shorts and Fabrics, J. Allergy **14**:477, 1943.

83. Costello, M. J., and Ryan, J. E.: Dermatitis from Underwear Shorts Processed by Resin Finishes: Report of Twenty Cases Observed at Bellevue Hospital, Arch. Dermat. & Syph. **46**:254 (Aug.) 1942.

84. Goldsmith, N. R.: Dermatitis from Semecarpus Anacardium (Bhilawanol or the Marking Nut), J. A. M. A. **123**:27 (Sept. 4) 1943.

85. Petro, J.: Respirator Dermatitis, Brit. M. J. **1**: 631, 1942.

86. Fox, E. C.: Mesquite Wood Dermatitis, Arch. Derm. & Syph. **44**:1098 (Dec.) 1941.

87. Cope, E. P.: Contact Dermatitis Due to Cod Liver Oil: Report of a Case, Arch. Dermat. & Syph. **46**:140 (July) 1942.

88. Simon, F. A.: Nail Polish Eczema, South. M. J. **36**:157, 1943.

89. Howell, J. B.: Contact Dermatitis from Hair Lacquer, J. A. M. A. **123**:408 (Oct. 16) 1943.

90. Epstein, S.: Contact Dermatitis Caused by Hair Lacquer Pads: A Characteristic Clinical Picture, J. A. M. A. **123**:409 (Oct. 16) 1943.

Stokes gave a lecture[91] full of common sense and good advice to Army surgeons on infections of the hands and feet and referred particularly to the dermatitis which certain surgeons acquire from certain kinds of rubber gloves. He recommended huge doses of D.G.A.D. (Don't give a damn), "that psychologic soporific which reduces the eternal friction between what one feels he must do and what one thinks he can." In other words, he felt that tension, fatigue and "poor condition" were aggravating factors even of a local disease like contact dermatitis.

GENERALIZED CUTANEOUS REACTIONS; DRUG ALLERGY

Of greater and more exciting interest, if not of more practical importance, is a group of cases in which drugs have caused generalized symptoms of all sorts. These reactions have been reviewed repeatedly, but the literature still contains reports of new cases due to new drugs or combinations of drugs. Barefoot and Callaway[92] give an excellent review of the literature on barbital poisoning. The barbiturates were introduced in 1913, and during the first fifteen years of their use only 41 instances of untoward reaction were found in the literature. In the second fifteen year period, however, the authors find 13 cases of exfoliative dermatitis due to phenobarbital, of which 10 were fatal. Their own case which they describe illustrates the unusual occurrence of trouble after relatively small doses of phenobarbital. A woman of 58 had taken only 32 mg. (½ grain) of phenobarbital three times a day, and only for ten days, before her face became "sunburned." The next day her whole skin became red, and a week later it began to exfoliate. She stayed in the hospital for thirty-five days before she could be discharged as well. A month later she took exactly 1 pill of phenobarbital and the next day she became red and soon went through the whole illness all over again, her skin desquamating completely. As the authors say, she is now convinced that phenobarbital is not good for her!

Thomas and Fenton[93] describe 9 cases in which pontocaine, used locally for bronchoscopy in 4 instances, for tooth extraction in 1 and for gastroscopy in 4, produced extremely severe reactions, which were fatal in 3 of the cases. After that experience use of pontocaine was discontinued at the Cleveland Clinic.

Diethylstilbestrol can cause trouble. Kasselberg[94] reports on a patient in whom generalized exfoliative dermatitis developed after the last of three weekly doses of the drug. Later skin tests elicited a strong immediate reaction with pseudopod formation. Saphir and Weinglass[95] write of a case in which a woman received 0.5 mg. of diethylstilbestrol each night and after five days pitting edema of both hands developed and then edema of the face and neck with laryngeal stridor. In this case, too, a skin test with a 1:2,000 dilution of diethylstilbestrol in water resulted in a tremendous immediate local urticarial reaction. Amphetamine sulfate caused a severe toxic reaction in a patient described by Kauvar, Henschel and Ravin.[96] In this case the reactions to skin tests were negative.

Saunders[97] reports his own experience of trouble from inhaling dry powdered neoarsphenamine. For some years he had been opening ampules to prepare solutions for his patients, and recently he found that within a minute or two he began to sneeze and his nose began to run. Skin tests made even by the scratch method with a 6 per cent solution of neoarsphenamine caused not only an extensive local reaction but in a few moments a general reaction with asthma—evidently analogous to the general reactions which occur from time to time in the treatment of any large group of patients with hay fever.

Two cases of sensitivity to quinine are reported by Rose.[98] In both patients a generalized erythematous eruption with swelling of the genitals developed after ingestion of 2 tablets of quinine bisulfate. Previously both patients had suffered reactions of the genitals following the use of contraceptives.

Diodrast is an iodine compound used freely in making roentgen studies of the renal pelvis.

91. Stokes, J. H., and Lee, W. E.: Contact, Contact-Infective and Infective-Allergic Dermatitis of the Hands, J. A. M. A. **123**:195 (Sept. 25) 1943.

92. Barefoot, S. W., and Callaway, J. L.: Exfoliative Dermatitis Due to Phenobarbital: Report of a Case with Recovery, Ann. Int. Med. **18**:105, 1943.

93. Thomas, J. W., and Fenton, M. M.: Fatalities and Constitutional Reactions Following the Use of Pontocaine, J. Allergy **14**:145, 1943.

94. Kasselberg, L. A.: Case of Exfoliative Dermatitis Due to Diethylstilbestrol, J. A. M. A. **120**:117 (Sept. 12) 1942.

95. Saphir, W., and Weinglass, A. R.: Severe Angioneurotic Edema Following Diethylstilbestrol Therapy, J. A. M. A. **119**:557 (June 13) 1942.

96. Kauvar, S. S.; Henschel, E. J., and Ravin, A.: Toxic Eruption Due to Amphetamine Sulfate and Its Analogue Dextroamphetamine Sulfate, J. A. M. A. **122**:1073 (Aug. 14) 1943.

97. Saunders, T. S.: Respiratory Allergy from the Arsphenamines: Personal Case Report, J. Allergy **14**: 76, 1942.

98. Rose, M. M.: Two Cases of Quinine Sensitivity, M. J. Australia **1**:71, 1943.

Reactions to diodrast based on a sensitivity to the substance are not as uncommon as expected. In my review of the literature of 1942 [99] I commented on several reports of reactions to diodrast. Other reports are noted this year; the subject is evidently important. Last winter at the Massachusetts General Hospital a woman of 45 stopped breathing and became cyanotic within a minute or two after an intravenous injection of diodrast had begun. For a few moments her condition was precarious, but epinephrine was injected at once and she recovered. She had a chronic pyelitis, and roentgen studies with use of diodrast had been made before. She recalled that she had felt chilly and weak after the last two examinations. How often does diodrast cause slight symptoms? Evidently they are easy to overlook. In this case no one appreciated that the patient might have become sensitized by the previous treatment. No one asked about previous reactions. Archer and Harris [100] say that instillation of a drop of diodrast solution into the eye is an easy test for sensitiveness which has proved effective in over 600 unselected cases. Robins [101] made skin tests with diodrast by injecting a small quantity of the drug solution from the ampule intracutaneously in 240 cases. The results of this test, however, were not too good. Thirty per cent of the patients who had systemic reactions did not have positive reactions to skin tests, and, on the other hand, only 24 per cent of those who had positive reactions to skin tests had systemic reactions.

Reactions to sulfonamide compounds are always important. The incidence is not great, but when reactions do occur they are apt to be so severe that the possibility of producing them should not be overlooked. Raffetto and Nichols [102] gave sulfadiazine to a 10 year old girl in a course of treatment lasting for eight days. The child improved, and for four days use of the drug was omitted. Later, however, it was given again, and within two days a violent reaction involving the skin, the eyes, and the throat took place and the child almost died. The eosinophil count of the blood rose to 23 per cent. The time relationships should be noted in connection with Longcope's paper, to be discussed later. The interval of four days without treatment may or may not be important. The fact is that the reaction occurred fourteen days after the first dose had been given.

Hurd and Jacox [103] describe 2 cases of thrombopenic purpura which developed as a complication of treatment with sulfathiazole and sulfadiazine respectively. Both patients were old people in whom nosebleeds and purpuric spots developed, whose blood cells dropped from high to a low level and who needed multiple transfusions, in spite of which one of them died.

In *The Journal of the American Medical Association* are a series of case reports which are of considerable interest in connection with the use of sulfonamide drugs incorporated into ointments. Livingood and Pillsbury [104] in the Army used a 5 per cent sulfathiazole cream for various local infections of the skin in something over a thousand cases. In 12 cases reactions occurred, not at the time when the cream was applied but shortly afterward, when the drug was given by mouth for some new condition. Three of the 12 cases are described in detail. The sulfathiazole cream had been applied for approximately two weeks, and then after an interval, which was five days in 1 case, twelve days in another and fifty-eight days in the third case, sulfathiazole was given by mouth. Within three to eight hours each of the 3 patients had chills and fever with malaise and a generalized vesicular eruption. The authors recommend that local sulfathiazole therapy should not be used for more than five days at a time and that the indications for it should be considered carefully, if only because the local treatment is capable of producing a generalized sensitiveness which may jeopardize the patient's life if later he needs the drug for some serious general disease.

Cohen, Thomas and Kalisch [105] describe 2 patients with varicose eczema who were treated with sulfathiazole ointment and in whom fever and toxic rashes developed simply from the local absorption. They conclude that "sulfathiazole is potentially too dangerous to use indiscriminately in mild ailments."

99. Rackemann, F. M.: Allergy: A Review of the Literature of 1942, Arch. Int. Med. **71**:107 (Jan.) 1943.

100. Archer, V. W., and Harris, I. D.: An Ocular Test for Sensitivity to Diodrast Prior to Intravenous Urography, Am. J. Roentgenol. **48**:763, 1942.

101. Robins, S. A.: Hypersensitivity to Diodrast as Determined by Skin Tests, Am. J. Roentgenol. **48**:766, 1942.

102. Raffetto, J. F., and Nichols, S.: A Nearly Fatal Reaction to Sulfadiazine in a Ten-Year-Old Girl Involving Skin, Eyes and Oropharynx, J. Pediat. **20**: 753. 1942.

103. Hurd, R. W., and Jacox, R. F.: Thrombopenic Purpura Developing as a Complication of Sulfathiazole and Sulfadiazine Therapy, J. A. M. A. **122**:296 (May 29) 1943.

104. Livingood, C. S., and Pillsbury, D. M.: Sulfathiazole in Eczematous Pyoderma, J. A. M. A. **121**: 406 (Feb. 6) 1943.

105. Cohen, M. H.; Thomas, H. B., and Kalisch, A. C.: Hypersensitivity Produced by the Topical Application of Sulfathiazole, J. A. M. A. **121**:408 (Feb. 6) 1943.

Weiner[106] also had 4 patients who showed extreme local hypersensitivity to sulfathiazole. Each of them gave positive reactions to patch tests with the drug crystals, and in each the dermatitis cleared when the treatment was omitted.

Shaffer, Lentz and McGuire[107] exhibit excellent pictures of the generalized cutaneous lesions, some of them bullous, which may result from sensitization to sulfathiazole. They point out that the condition may be induced by the local application and be elicited later by oral exhibition. In a report of the Council on Pharmacy and Chemistry, Cole[108] declares that: "Despite its value in some cases, the evidence of usefulness of sulfonamide compounds in dermatology is insufficient to justify their inclusion in New and Nonofficial Remedies." As he said: "The sulfonamides act well in powder form, but should not be used until other measures fail. They should not be used for more than five days at a time, and their use should be limited to those cases in which the drug is prescribed by the doctor himself."

Weiner[109] draws further attention to the importance of eruptions due to sulfathiazole. He repeats that sensitization may develop from local application or from ingestion of the drug. When the drug is given again, the eruptions may be of the contact type, in which patch tests elicit positive reactions, or of the generalized disseminated variety, in which reactions to skin tests of the immediate type and/or passive transfer antibodies (reagins) may be occasionally demonstrated in the patient's serum. In sensitization to sulfonamide compounds the two types of allergy, local and general, can exist either singly or together.

The whole subject of reactions to drugs, particularly to the sulfonamide compounds, has been reviewed in a clear, masterly paper by Longcope.[110] A good many of the responses can be compared easily to the reaction to foreign serum called "serum sickness." Longcope points out that different antigens vary in their ability to produce serum sickness and that the antigenic property can be increased by the addition of antibodies (immune serum is more likely to cause trouble than is normal serum) as well as by the admixture of bacterial filtrates and other products. It can be diminished somewhat by purification of the serum. "Despeciation" by treatment of the serum by heat, by acid or by alkali is sometimes helpful but may reduce the antibody content at the same time. Specificity is determined always by the chemical constitution, as Landsteiner has demonstrated. Reactions to drugs are often comparable to serum sickness. "Nirvanol," for example, is a sodium salt of phenylethylhydantoin. The drug is used in treatment of chorea, and it is not uncommon to have "nirvanol sickness" begin within six days after administration of the drug is started. It is as well defined as measles. Curiously, however, a second course of the drug rarely causes an immediate reaction. Cutaneous sensitivity cannot be demonstrated; no antibodies are found. Milian's erythema of the ninth day is a rash which may appear on the ninth or tenth day after a dose of neoarsphenamine. It also is analogous to serum sickness, and subsequent treatment may lead to serious reaction. As Dr. Longcope says, prevention of these disturbing symptom complexes consists, first, in thinking of the possibility; second, in asking the patient about his previous experiences with that substance, and, third, in making sure that the treatment is indicated and necessary. Reactions to eye tests and skin tests are interesting, but if the intravenous injection is given slowly and carefully, with an eye to the first signs of reaction, serious trouble will be avoided. Once the reaction of "serum sickness" has developed, there is no treatment which is really successful. Epinephrine is the best immediate symptomatic remedy.

Atopic Eczema.—Eczema of the atopic type, so called neurodermatitis, may be due in part at least to a dietary deficiency. Burr[111] observed that when rats were fed on a diet from which all fat was excluded the skin became scaly, with necrosis of the tail, growth was retarded, lesions developed in the kidneys and the animals died. The feeding of fatty acids relieved the condition at once, and the fatty acids were more effective as they were more unsaturated. As might be expected, the skin did not clear unless growth and nutri-

106. Weiner, A. L.: Cutaneous Hypersensitivity to Topical Application of Sulfathiazole, J. A. M. A. **121**:411 (Feb. 6) 1943.

107. Shaffer, B.; Lentz, J. W., and McGuire, J. A.: Sulfathiazole Eruptions: Sensitivity Induced by Local Therapy and Elicited by Oral Medication: Report of Four Cases with Some Allergic Studies, J. A. M. A. **123**:17 (Sept. 4) 1943.

108. Cole, H. N.: The Local Use of Sulfonamide Compounds in Dermatology, report of the Council on Pharmacy and Chemistry, J. A. M. A. **123**:411 (Oct. 16) 1943.

109. Weiner, A. L.: Cutaneous Eruptions Following Topical and Oral Sulfathiazole, correspondence, J. A. M. A. **123**:436 (Oct. 16) 1943.

110. Longcope, W. T.: Serum Sickness and Analogous Reactions from Certain Drugs, Particularly the Sulfonamides, Medicine **22**:251, 1943.

111. Burr, G. D.: Significance of the Essential Fatty Acids, Federation **1**:224, 1942.

tion were improved at the same time. In his paper is the picture of an infant with severe facial eczema. He was given 3 teaspoons of lard each day for a month, and the next picture shows his skin clear. The relations between various fatty acids, their sparing action one on the other and their relation to other vitamins are discussed. Di Sant'Agnese and Larkin [112] studied the capacity for absorption of vitamin A in 4 infants with eczema and found it greatly impaired. Deficiency may depend on faulty absorption as well as on inadequate feeding. Harris and Gay [113] treated 20 patients with infantile eczema with large doses of vitamin B (whole complex), but only 2 patients were healed, although 11 others were improved. Engman and MacCardle [114] found a new approach to the problem: They fed white rats on a magnesium-deficient diet and report that cutaneous lesions similar to those of neurodermatitis developed.

The relation between these deficiencies and the capacity to acquire sensitiveness must be considered, if only because there are so many cases in which a simple food allergy, to eggs or to cows' milk for example, appears to be an adequate cause for the disease. Skin tests elicit positive reactions; the food is eliminated; the child recovers. Whether this sensitization is conditioned by the total dietary and its proper absorption is a good question. Frei [115] studied the effect of variations in the vitamin A (carotene) intake and the development of hypersensitiveness to arsphenamine in guinea pigs, but he could find no variation in the degree of reactions before and after the treatment. This, however, was an "acute" experiment. McKhann, Spector and Meserve [116] in an excellent review on the celiac syndrome say that it is not clear whether the allergy is secondary to the gastrointestinal symptoms or vice versa. It is their impression that the difficulty with the absorption of fat is a result of the allergy and not a cause of it. Fries and Mogil [117] took roentgenograms of children with the symptoms of gastrointestinal allergy. Gastric retention was the most common finding, but increased intestinal segmentation and colonic spasm were also observed. They say that these effects were not due to the nutritive composition of the food, but then they admit that flavorings in even small amounts may produce changes. Wing and co-workers [118] studied food allergy with the roentgen rays both in man and in the guinea pig. In the cases of 3 of 9 patients they felt sure that the abnormalities observed were not due to the nutritive factors, but obviously the method is hard to control. This subject of infantile eczema and of neurodermatitis is important. There is neither time nor space to discuss it further here, but it is good to have several new suggestions as leads for further study.

MÉNIÈRE'S DISEASE AND MIGRAINE

Atkinson [119] has written a helpful paper on the relation between Ménière's disease and migraine. The auditory artery and the posterior cerebral artery are both branches of the basilar artery. It is easy to see how the vertigo of Ménière's disease and the scotoma of migraine can have a similar mechanism and be related. As said before, in the paragraphs on the chemical effectors, Atkinson distinguished between persons who have headaches of the vasodilator type ("red headaches"), a small group, with symptoms sometimes precipitated by allergy, sensitive to histamine and relieved by treatment with histamine, and persons with headaches of the vasoconstrictor type ("white headaches"), a much larger group, with no allergy, not sensitive to histamine and relieved by nicotinic acid. Combinations of headaches and dizziness are common, and one finds "migraine with vertigo" or "Ménière's syndrome with headache." The frequency is shown in a tabulation adapted from Atkinson's paper:

Ménière's Disease

	Vasodilator Group	Vasoconstrictor Group
With migraine	10	12
With nonspecific headache	6	36
No headache	4	40
Total	20	88

112. di Sant'Agnese, P. A., and Larkin, V. deP.: Vitamin A Absorption in Infantile Eczema, Proc. Soc. Exper. Biol. & Med. **52**:343, 1943.

113. Harris, A., and Gay, L. N.: The Use of Vitamin B Complex in the Treatment of Infantile Eczema, J. Allergy **14**:182, 1943.

114. Engman, M. F., Jr., and MacCardle, R. C.: A New Approach to the Problem of a Disseminated Neurodermatitis, Arch. Dermat. & Syph. **46**:337 (Sept.) 1943.

115. Frei, W.: Further Studies in Arsphenamine Hypersensitiveness in Guinea Pigs: IV. Vitamin A (Carotene) in Relation to the Sensitization of Guinea Pigs to Old Arsphenamine, J. Invest. Dermat. **5**:117, 1942.

116. McKhann, C. F.; Spector, S., and Meserve, E. R.: An Association of Gastro-Intestinal Allergy with the Celiac Syndrome, J. Pediat. **22**:362, 1943.

117. Fries, J. H., and Mogil, M.: Roentgen Observations on Children with Gastrointestinal Allergy to Foods, J. Allergy **14**:310, 1943.

118. Wing, W. M.; Smith, C.; Borne, W. H., and Cooke, R. A.: Spontaneous and Induced Sensitivity to Food Stuffs: X-Ray Studies of the Small Intestine in Man and Guinea Pig, J. Allergy **14**:56, 1942.

119. Atkinson, M.: Ménière's Syndrome and Migraine: Observations on a Common Causal Relationship, Ann. Int. Med. **18**:797, 1943.

The history is helpful, for in the vasodilator group the headache comes first, before the dizziness, which often "explodes" in a sudden attack, while in the vasoconstrictor group the vertigo comes first, with headache later. Meantime, Trowbridge and co-workers [120] find that the conventional methods of symptomatic treatment of migraine are effective so far as the one attack is concerned: Ergotamine tartrate gave complete relief in 80 per cent of the cases in which it was used. Morphine was effective in 59 per cent, phenobarbital in 16 per cent and acetylsalicylic acid in 10 per cent.

INSULIN ALLERGY

Insulin allergy may be a troublesome complication. Goldner and Ricketts [121] found that 20 per cent of patients treated with insulin manifest mild local reactions after the first week of treatment, which, however, disappear as the treatment continues. In 8 cases the sensitiveness persisted or developed at a later time. This was especially the case when the patient had neglected to take insulin regularly and when the time interval was sufficient to allow the sensitizing effect of the early treatment to develop. The lapse in therapy was important. Prevention of further local reaction was effected by injecting insulin in small increasing doses at intervals of only a few hours. Watson [122] found insulin allergy in 5 per cent of his insulin-treated diabetic patients. Weitz [123] describes a patient whom he had desensitized successfully and adds that the positive reactions to skin tests and the antibodies (reagins) to insulin which were present at the start disappeared later. Lowell [124] has found two antibodies for crystalline insulin. One is concerned with the allergy and, like other reagins, is destroyed by heating the serum at 56 C. for an hour: the other is concerned with resistance to insulin. A patient who gave a positive reaction to a skin test with insulin showed no reduction of the blood sugar level when crystalline insulin was injected. Her tolerance to crystalline insulin was abnormally high. Her serum protected mice against lethal doses of crystalline insulin. Toward human insulin she behaved differently. The skin test elicited a positive reaction as before, but the blood sugar level dropped when human insulin was given. Her tolerance for human insulin was normal. Her serum was not effective in protecting mice against human insulin. The reason for the discrepancy is hard to explain.

ALLERGY TO INJECTABLE LIVER EXTRACTS

Feinberg, Howard and Young [125] add 8 cases to the list of 29 reviewed in 1940 by Harten and Walzer.[126] They made skin tests on their patients with ten different commercial preparations of liver; they also applied fresh juices from beef, hog, horse and human livers and extracts of other organs. All their patients reacted to the purified liver extracts but not to the proteins of muscle, kidney or stomach except for slight responses in 1 or 2 instances. The authors conclude that the allergy is directed to the antianemic factor in the liver and that this is a potent allergen which contains neither protein nor carbohydrate and which is not species specific or organ specific. I quote: "Attention is called to the potential immunologic significance of the demonstration of an antigen residing in a fraction of an organ tissue."

INSECT BITES

There are three reports dealing with severe reactions to insect bites. From Kenya Colony comes the report of Jex-Blake [127] that a patient was stung by bees twelve times during twenty years with no ill effects. Then, after another bee sting he became acutely ill, pulseless, cyanotic and unconscious for about ten minutes. Nine months later he was bitten again, and this time he died within fifteen minutes. Similar is the case reported by Helm.[128]

Mease [129] describes a man working in a Florida orange grove, where he was miserable because of severe reaction to the bites of deer flies. Thirty flies were collected and macerated in 30 cc. of buffered saline solution, and skin tests with the filtered extract were made on the patient as well as on normal persons. The normal persons gave

120. Trowbridge, L. S.; von Storch, T. J. C., and Moore, M.: The Drug Therapy of Migraine Headache, New England J. Med. **227**:699, 1942.

121. Goldner, M. G., and Ricketts, H. T.: Insulin Allergy: A Report of Eight Cases with Generalized Symptoms, J. Clin. Endocrinol. **2**:595, 1942.

122. Watson, E. M.: Nonhypoglycemic (Allergic) Insulin Reactions, Canad. M. A. J. **47**:336, 1942.

123. Weitz, M. A.: Insulin Hypersensitivity with Desensitization, J. Allergy **14**:220, 1943.

124. Lowell, F. C.: Evidence for the Existence of Two Antibodies for Crystalline Insulin, Proc. Soc. Exper. Biol. & Med. **50**:167, 1942.

125. Feinberg, S. M.; Howard, L. A., and Young, R. H.: Allergy to Injectable Liver Extracts: Clinical and Immunological Observations, Ann. Int. Med. **18**:311, 1943.

126. Harten, M., and Walzer, M.: Annual Review: Allergy to Insulin, Liver, Pituitary, Pancreas, Estrogens, Enzymes, and Similar Substances, J. Allergy **12**: 72, 1940.

127. Jex-Blake, A. J.: Bee Stings in Kenya Colony, Brit. M. J. **2**:241, 1942.

128. Helm, S.: Severe Anaphylactic Reaction to Bee or Wasp Sting, Mil. Surgeon **92**:64, 1943.

129. Mease, J. A.: Deer Fly Desensitization, J. A. M. A. **122**:227 (May 22) 1943.

no reaction, but the patient gave an immediate urticarial wheal response. In view of this, desensitization was carried out. The man was treated with doses of the extract given subcutaneously on the second, fourth, seventh and eleventh days and thereafter for ten weekly intervals. Meantime, the flies no longer bothered him. The next spring he was given more injections, and since then for four years he has been "cured."

Longcope [110] compares reactions to drugs to serum disease. It is easy to compare other and even more dramatic episodes to anaphylaxis itself. In these there are three factors: first, the original treatment, which may be likened to the sensitizing dose; second, a period of time without treatment, the incubation period, and, third, the subsequent dose, which is followed often and promptly by a severe and literally shocking reaction. This sequence occurs in some of the cases of reaction to drugs: Sulfonamide drugs are given for gonorrhea at the age of 26 and no trouble results, but when such compounds are given again to the same man for pneumonia or meningitis at the age of 32 severe symptoms develop at once. This occurs with insulin and with liver preparations and with insect bites. Is it possible that other allergies, like hay fever or hypersensitivities to dogs or cats, are aggravated by the fact that exposure is intermittent, sometimes with years between the periods of contact?

As for our boys overseas, thank God that each and every one of them has been immunized actively with diphtheria and tetanus toxoids and with gas bacillus vaccine and that many have been immunized with the yellow fever virus. Foreign serum is no longer to be reckoned with except in odd cases. Reactions to human plasma are reported and will be reviewed later when more is known about them. This is no time to cast any aspersion on a method which has saved so many lives but one can hope that the study of these reactions which is going on all over the world will lead to still greater advances in knowledge.

263 Beacon Street.

Book Reviews

Gastro-enterology. By Henry L. Bockus, M.D. Volume I. Price, $12. Pp. 831. Philadelphia: W. B. Saunders Co., 1943.

The first volume of what promises to be a monumental work on gastroenterology discusses the esophagus and the stomach. Volume II is to deal with the small and large intestines and the peritoneum, and volume III, with the liver, the biliary tract and the pancreas.

The book makes its beginning, in section I, with five chapters on the examination of the patient. The first chapter has to do with history taking, and in view of the detailed discussion of diseases of the stomach and the esophagus elsewhere it would seem that the ten pages devoted to history taking is rather brief. In this section the other chapters have to do with symptomatology, with the physical examination and with the laboratory examinations.

Section II has to do with the esophagus and the diaphragm. Eleven chapters are devoted to applied anatomy and physiology of the esophagus, stricture, cardiospasm, tumors, esophageal hiatus hernia and so on.

Section III, on disorders of the stomach, makes up the bulk of the volume, 624 pages. It is readily appreciated, therefore, that the subject is covered with minute attention to every phase. The introductory chapters have to do with the applied anatomy and physiology of the stomach, but the remainder of the section is devoted to the pathology, the diagnosis and the treatment of various gastric diseases.

Only the most favorable comments can be made about this tremendous undertaking of Dr. Bockus. The book is the product of an ingenious, fertile and retentive mind. One of the agreeable features of the book is that Bockus uses the first person singular repeatedly and expresses his own definite opinions about nearly everything he discusses. Most readers appreciate the personal touch in their reading. One minor criticism is that Bockus is not quite sure when a patient is a patient or a case. As a rule one treats a patient rather than a case; the patient dies and not the case.

The format in every way is excellent. The paper is glossy and permits of excellent reproduction of roentgenograms, drawings and photographs. Some of the photographs, incidentally, are colored. This first volume is well indexed, and there are innumerable references. The book can be recommended not only for its excellent appearance but, what is much more important, for its intelligent and thoughtful presentation. It should appeal to the internist irrespective of whether or not he classifies himself as a gastroenterologist. It should be on his bookshelf. Surgeons and other specialists who may have occasional problems dealing with the gastrointestinal tract would probably consult it frequently in a medical library in order to have an authoritative and last word observation on a subject in which they are probably only remotely interested.

Pathology and Therapy of Rheumatic Fever. By Leopold Lichtwitz, M.D. Foreword by William J. Maloney, M.D., LL.D., F.R.S. (Edin). Edited by Major William Chester, M. C., A. U. S. Price, $4.75. Pp. 211. New York: Grune and Stratton, 1944.

For many years rheumatic fever has been the subject of profound and tireless investigation by eminent clinicians, bacteriologists, pathologists, public health workers and other investigators. While much progress has been achieved toward a better understanding of the disease, it is generally conceded that the causation of rheumatic fever is still unsettled but that several factors participate. It is therefore amazing to note the uncompromising views expressed by the author of this text. The opening sentence of the book clearly depicts this: "Rheumatic fever is a noninfectious disease." The author contends that rheumatic fever is caused, not by a specific micro-organism or virus, but by a sensitization to antigens, protein in nature, which in most cases are products of micro-organisms. All consequent arguments are based on this premise.

The conventional ideas of incidence and personal factors of rheumatic fever are considered. The pathologic changes of the disease as they occur in various parts of the body are discussed in considerable detail. The author states that Aschoff bodies are neither specific to rheumatic fever nor pathognomonic of it and briefly dismisses the controversial issue regarding what he calls analogous lesions. He writes that such lesions occur in other infectious diseases. In the last paragraph on page 42 is found the following remarkable statement: "The collagen fibrils swell, and the auricular endothelium, losing its epithelium, undergoes necrosis." It is possible that the word epithelium is a typographic error.

All possible forms of therapy are discussed in detail. Tonsillectomy is condemned, but the local treatment of infected tonsils, a method long since frowned on by leading otolaryngologists, is advocated. While tonsillectomy neither cures nor prevents rheumatic fever, definite indications for its performance frequently occur.

The reviewer is fully aware of the uncertainties that prevail today regarding the causation of rheumatic fever and therefore cannot subscribe to the unequivocal views expressed in this book. The allergic factor in rheumatic fever is generally accepted, but with the evidence at hand it cannot be looked on as the sole cause. The book contains numerous inconsistencies and contradictions.

The Role of Nutritional Deficiency in Nervous and Mental Disease. Research Publications, Association for Research in Nervous and Mental Disease. Volume XXII. Price, $4. Pp. 215. Baltimore: Williams & Wilkins Company, 1943.

This excellent book of two hundred pages consists of the proceedings of the December 1941 meeting of the Association for Research in Nervous and Mental Disease. It is a symposium on the role of nutritional deficiency in neuropsychiatric disorders and includes sixteen articles, each of which was contributed by an expert in his particular field of endeavor. The first half of the volume is devoted to papers which summarize contributions from the fundamental sciences; the second, to reports on clinical aspects of the subject. The opening chapters are of general interest, the first containing a brief discussion of outstanding facts gleaned from physiologic investigations of animal nutrition and the second dealing with the relation of enzymes to deficiency disease. Subsequent articles are devoted to the role of vitamins in brain metabolism, general problems of nutritional deficiency, the thiamine content of human tissue,

the pathology of deficiencies of the vitamin B group, vitamin A and the nervous system and vitamin E deprivation. The second part of the book includes discussions of the clinical aspects of human thiamine deficiency, experimentally induced, mental and neurologic aspects of vitamin B complex deficiencies, emotional disturbances in pellagra, multiple neuritis, phenylpyruvic oligophrenia, pernicious anemia and allied disorders, the psychoses and nutritional deficiency, and the prevention and cure of nutritive failure.

Appended to each article is the discussion which followed presentation of the paper. This is exceedingly valuable in clarifying, and often resolving, apparently inconsistent findings and in presenting the rationale of divergent opinions on a number of controversial subjects.

The book is highly recommended, not only to the neuropsychiatrist but to all clinicians interested in the general problems of deficiency disease.

Office Treatment of the Nose, Throat and Ear. By A. R. Hollender, M.D., Associate Professor of Laryngology, Rhinology and Otology, University of Illinois College of Medicine. Price, $5. Pp. 480, with 120 illustrations. Chicago: Year Book Publishers, Inc., 1943.

This is an attractive book which physicians and medical students will be glad to know. The author says that a large number of diseases of the nose, throat and ear should be treated at the office rather than in the hospital, and he proceeds to describe each of these and how they should be managed.

He has divided his subject-matter into two parts: The first gives a general survey of the field and an account of the available therapeutic measures; the second describes technics to be utilized. The whole makes up an excellent handbook, practical as can be.

The illustrations in the technical section are unusually good, so that one can readily see how the different tools that the modern otolaryngologist has at his command should be manipulated. The writing throughout is simple and unaffected, and the author's meaning is always understandable. At the end of each of the twenty-three chapters is a short bibliography selected critically to develop further information around the topics discussed.

The methods of treatment which are advocated often seem relatively simple, are described in detail and appear to be based on a solid foundation of common sense and experience. On the whole, here is a book that a great many physicians will find useful; and students or interns will swear by it.

A Textbook of Medicine. By American Authors. Edited by Russell L. Cecil, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College. Associate Editor for Diseases of the Nervous System, Foster Kennedy, M.D., F.R.S.E., Professor of Clinical Neurology, Cornell University Medical College. Sixth Edition, Revised and Entirely Reset. Price, $9.50. Pp. 1,566, with 195 illustrations and charts. Philadelphia: W. B. Saunders Company, 1943.

One hundred and fifty-four authors have collaborated under the editorship of Drs. Cecil and Kennedy to produce this book. It is the sixth edition of this well known textbook, which first appeared in 1927. Any work that goes through six editions in fifteen years may be accepted as worth while. The book is familiar to most physicians, but the present edition contains much that is new and much that has been thoroughly rewritten. Aviation medicine, air sickness, virus pneumonia and hirudinea represent a few of the innovations. The form of the book has been changed so that much new material has been added without increasing the already large size too much. As a matter of fact, there are fewer pages, but the larger page size and the arrangement of the material in double columns more than make up for that.

This work still remains a standard one for students, teachers and practitioners.

Modificacoes de forma do eletrocardiograma. By Dante Pazzanese. Pp. 373. São Paulo, Brazil: Grafica da Prefeitura, 1942.

The author emphasizes the importance of employing a proper technic when recording an electrocardiogram. He presents tracings showing patterns characteristic of infarction that are due to technical errors. Several such types of tracings are presented throughout the monograph to emphasize the importance of controlling technic, variations in the patient's habitus and certain normal physiologic phenomena when interpreting electrocardiograms. Some of the records are interesting.

There are many illustrations. Most of them are clear, but too many are poor. The author approaches the problem in more or less the same fashion as followed in other monographs. He does not employ any new or truly original lines of presentation. As in most monographs on the subject, there is no simplification of the subject. The book fails to fulfil the needs of a beginner who is interested in electrocardiography for the first time. There is little of interest to one who is already trained in the subject; to him the volume is just another book on electrocardiography. It does, however, fulfil a need in that it makes a monograph on the subject available to physicians who are better acquainted with the Portuguese language than with English.

Pain. By thirty-seven contributors. Research Publications of the Association for Research in Nervous and Mental Disease. Volume XXIII. Price, $7.50. Pp. 468. Baltimore: Williams & Wilkins Company, 1943.

This volume maintains the high standards set by the previous research publications. In 1942 the subject of pain was selected as the topic for the annual meeting of the organization. Thirty-seven different contributors, with associates in some instances, have made possible a 468 page discussion of what is, to make a trite statement, the most important symptom subjectively in the category of symptoms, namely pain. This "simple sensory experience" is discussed from innumerable points of view. The symposium starts out with a physiologic and psychologic discussion of pain and continues more specifically in the field of special types of pain, such as those that occur in heart disease, in headache and in diseases of the digestive tract and of other important organs and systems of the body. Altogether the subject of pain is treated in a comprehensive fashion, and the reader of this publication will obtain a broad knowledge of what pain is, how pain expresses itself, what can be done for painful conditions, how important pain is in diagnosis and so on ad infinitum. The reviewer considers this book to be an important contribution and recommends it most highly.

Internal Medicine in General Practice. By Lieutenant Robert Pratt McCombs (MC) U.S.N.R., recently Instructor in Internal Medicine for the Statewide Postgraduate Program of the Tennessee State Medical Association. Price, cloth, $7. Pp. 694, with 114 illustrations and figures. Philadelphia: W. B. Saunders Company, 1943.

This is a textbook of medicine that begins at a little higher level than the textbook for students. It attempts to do what the title indicates, namely, to present a postgraduate course in medicine for general practitioners. It does this reasonably well. It covers a surprisingly wide range of subjects in a rather abbreviated fashion and points out the salient diagnostic features of and the therapeutic pitfalls that lie in various diseases. It reviews the detail of history taking and of physical diagnosis and is well up-to-date on its coverage of new disease entities and new therapeutic agents. The book will be of considerable value to the busy wartime general practitioner, and it is pointed out in the foreword that it may serve a purpose among physicians in the armed services when they are called on to meet situations with which they are not entirely familiar.

The Compleat Pediatrician. By Wilbur C. Davison, M.D., Professor of Pediatrics, Duke University School of Medicine. Price, $3.75. Durham, N. C.: Duke University Press, 1943.

The "Compleat Pediatrician" fills the same admirable purpose in this edition that it has in three earlier ones; it has no peer as a "bedside guidebook" for student and practitioner alike.

Many revisions have been made, all eminently practical and all designed to serve as stimulating *reminders* of a broader coverage of medical knowledge contained in larger, more conventional textbooks.

Only by a brief study of the volume can one appreciate its great usefulness; the division of subjects follows a logical order, and any one using the volume for the purpose intended will find it an invaluable aid. Brief descriptions and evaluations of newer laboratory procedures should be most helpful to busy practitioners.

This book should be on the desk or in the kit of any physician who deals with infants and children.

Elements of Medical Mycology. By Jacob Hyams Swartz. Price, $4.50. Pp. 190, with 80 illustrations and 1 chart. New York: Grune and Stratton, Inc., 1943.

The best part of this little manual is the systematic descriptions and illustrations of the various fungi. The clinical descriptions are too brief to be of a great deal of value, and here and there are statements with which the reviewer does not entirely agree. It is his impression, for example, that precipitation and complement fixation tests for coccidiodomycosis are now well established as diagnostic procedures. The book is finely printed and beautifully illustrated; there are bibliographies and an index, and on the whole it should prove useful as an introduction to the subject.

Applied Dietetics. By Frances Stern. Second edition. Price, $4. Pp. 267, with 57 tables. Baltimore: Williams & Wilkins Company, 1944.

Miss Stern stands out as a pioneer figure in modern dietetics; the preface of her book recalls that the food clinic at the Boston Dispensary was opened as long ago as 1918. It must be a source of gratification to the author, who worked so hard and for so many years to encourage others, to see the food clinic now universally recognized as an integral part of any outpatient department. Miss Stern's book contains the usual machinery of such compendiums—diet lists, tables of food values, etc. Special emphasis is on the normal diet and the environmental factors which influence it. Above all the education of the patient is stressed. It is a pleasure to welcome after nine years the appearance of a new edition of this useful book.

Clinical Lectures on the Gallbladder and Bile Ducts. By Samuel Weiss. Price, $5.50. Pp. 504, with 125 figures and 21 tables. Chicago: Year Book Publishers, Inc., 1944.

The method of dealing with a subject in a series of lectures takes one back to the nineteenth century, when it had a high degree of popularity. One may believe that the writer by assembling a series of lectures implies a somewhat informal discussion and perhaps relieves himself from the responsibility of systematically covering all aspects of a subject. Lectures may also be assumed to reflect a highly personal point of view. The present volume, however, covers the subjects of the gallbladder and the bile ducts thoroughly and adequately. The illustrations are profuse and well selected, and there are good bibliographies.

Handbook of Nutrition: A Symposium. Prepared by Council on Foods and Nutrition of American Medical Association. Price, $2.50. Pp. 586. Chicago: American Medical Association, 1943.

Most physicians have seen these excellent articles in *The Journal of the American Medical Association* as they have appeared during the past year or so. The subjects of nutrition in general, vitamins, vitamin deficiency and minerals in nutrition are thoroughly covered by outstanding authorities. The volume furnishes a mine of information as well as a thorough bibliography of the recent literature.

Medical Physics. Editor in Chief, Otto Glasser. Price, $18. Pp. 1744, with numerous figures and tables. Chicago: The Year Book Publishers, Inc., 1944.

This monumental compendium of 1,744 pages (folio) dealing with the application of physics in medicine is really a small encyclopedia. Alphabetically arranged there are hundreds of brief articles dealing with all sorts of subjects. Thus if one opens at random one comes across "Massage," "Mathematical Biophysics," "Matter: Structure," "Metabolism: Apparatus" and "Methods." A series of articles on "Roentgenography" runs from page 1262 to 1330, to be followed by 70 pages on "Roentgen Rays." Then comes "Shock," "Sound," etc. The articles are concise, written by well known authorities and plentifully illustrated with photographs, charts and tables. There are adequate indexes, and the material is easy to find. One is impressed by the need of just this sort of reference book.

Neurology. By Roy R. Grinker, M.D. Third edition. Price, $6.50. Pp. 1075. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

As a comprehensive textbook in one volume, this edition of "Neurology" is to be recommended above any other text. Previous editions are well known for the successful inclusion of fundamental anatomic and physiologic knowledge in a clinical book. This edition has followed the same policy but has improved on the

clinical discussions and has omitted none of the significant neurologic conditions. The latest in diagnostic and therapeutic technics are presented in good detail and are too numerous to be listed here. The book carries authority because of the writer's own studies on a wide range of neurologic problems.

This volume is well proportioned and intelligently written; it is therefore pleasant reading. It is a large book but is $2 cheaper than previous editions.

Primeras reuniones extraordinarias de la Asociacion de medicos del Hospital Durand. Edited by Dr. Jose Alberto Pique. Pp. 675 and 1428 (two volumes). Buenos Aires, Argentina, 1942.

These two volumes contain papers presented by the members of the staff of the Durand Hospital at the staff meetings held intermittently throughout the year. The selection of subjects is catholic; they extend from occupational diseases and glaucoma to therapeutic abortion and acute appendicitis. The articles might be welcomed by general practitioners, though the treatment of some of the subjects is probably far beyond their fundamental knowledge. The subjects in which specialists might be interested are few and far between. The book consequently is neither fish, fowl nor good red herring and would have a limited appeal to American physicians. It does show concretely, however, that a hospital staff can have excellent meetings and that they can be carried through in more than a perfunctory manner.

Family Nutrition. Published by the Philadelphia Child Health Society. Price, 50 cents. Pp. 119, with 22 tables, 10 charts and 26 illustrations. Philadelphia, 1943.

This brochure gives an admirable summary of the problems of nutrition. The usual facts about calories, vitamins, etc., are well stated, but in addition there is much useful material on the nutritional status of groups, diet in relation to public health problems and menu planning for various groups. The material is well organized, with excellent diagrams and charts.

CORRECTION

In the article by Captain John E. Leach entitled "Effect of Roentgen Therapy on the Heart: A Clinical Study," which appeared in the December 1943 issue (ARCH. INT. MED. **72**:715, 1943), the word "arrhythmia" is spelled, incorrectly, without the "h."